Essays in Health Economics: Welfare Analysis – Applied discrete choice analysis and cost-effectiveness and budget impact theory

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Chapter 1: Preface

After finishing my master studies in Economics I started to work as a Health Economic consultant for an international company located in Loerrach / Germany. After some months working there I started to think about a cumulative PhD thesis in the area of applied Discrete Choice Analysis and some issues I found in the economic evaluation methods.

I have to thank Prof. Peter Zweifel that he was that flexible to accept me as an external PhD student in April 2005. After some discussions with Rito Bergemann I wrote, together with him, a paper about possible biases in the current Cost-Effectiveness methods due to a possible wrong use of the discount rate (Chapter 1). At the same time Marcos Memran from New York, also a consultant, suggested that he can support me in collecting my own dataset for a discrete choice analysis in the US. I started to develop the questionnaire based on my knowledge I build due to extensive literature reading and my consulting work I have done with some of the biggest pharmaceutical companies. In March 2006 I received the whole dataset and I started to analyze these regarding preferences and willingness-to-pay (chapters 2 and 3). Additionally I analyzed the dataset regarding an issue called the “learning effect” in discrete choice analysis (chapter 4).

During discussions at the ISPOR (**I**nternational **S**ociety for **P**harmacoeconomics and **O**utcomes **R**esearch) congress 2005 in Florence about budget impact modeling, a relatively new feature in the economic evaluation tools, I had the idea that early retirement should have an influence on the decision making of a new pharmaceutical drug based on a budget impact analysis. I developed a theoretical framework for that and tested it in a hypothetical example in the diabetes area (chapter 5).

My sincere thanks also go to other former colleagues of mine: Luca Morlotti, who was always available for discussions and criticisms; Elvira Müller for her reviews and the time she gave me to do all my PhD courses within one year; Monika Neumann who did the formatting of my papers; Heather Falvey, Per-Olov Johansson and Mikael Svensson for their reviews of different papers.

Due to the fact that the biggest gratitude is always mentioned at the end, I want to thank my girl friend and future wife, Sabrina Wrobel, for allowing me to always count on her full support and encouragement during this endeavor. She had to bear the biggest burden due to the hours I

spent with my books, papers, datasets and discussions in nearly each second of my (rare) leisure time. However she always supported me without any ifs or buts.

Lörrach, November 2006 Stefan Walzer

Chapter 2: Introduction

The five essays offered in this monograph cover three topics in economic evaluations: The first essay is a theoretical investigation of a new cost-effectiveness analysis approach by using a variable discount rate over time for long-term and chronic diseases such as diabetes. The second and third essays address an empirical discrete choice analysis by showing first the preferences and then the willingness-to-pay for various characteristics of an asthma treatment for caregivers with children aged 4 years and younger. The fourth essay is an analysis whether a so-called learning effect can be proven within an empirical discrete choice approach.

The fifth essay, finally, belongs to the realm of budget impact modeling, a relatively new tool in the economic evaluation. It develops a theoretical model explaining the impact of early retirement on the decision-making based on such a model.

All five essays can be placed in the same region of economics. They are all based in the economic evaluations whereas different approaches were used or more developed. The cost-effectiveness analysis is widely used for the submission of drug and intervention/device appraisals for reimbursement or funding and/or price negotiations in various countries such as UK, Canada, Italy, Sweden and others. The conjoint analysis is more applied to derive the utilities and preferences of (potential) consumers. Furthermore the results of such a study, especially when using a willingness-to-pay approach could also be applied to a cost-benefit analysis. The budget impact approach was introduced to analyze the affordability of new drugs/interventions/devices for countries with a given budget. Usually budget impact analysis complements a cost-effectiveness or cost-benefit analysis. The five essays here are following a similar pathway. All five essays could be seen as a flow of a usual evaluation of a new drug/intervention/device. First a cost-effectiveness analysis, applying the new approach, could be performed before demand estimation and the drivers of demand are analyzed by applying a conjoint analysis. The willingness-to-pay of individuals is estimated whereas the potential bias by a learning effect could be neglected according to the findings here. Finally the budget impact analysis could complement the whole story by showing a third party payer the influence of the new drug/intervention/device on their (fixed) budget.

In the first essay the current approach of cost-effectiveness analysis especially for long-term diseases is criticized and a new approach is suggested: In cost-effectiveness analyses consensus exists among health economists regarding adjustment of discount rates with a constant and equal inflation rate for the time horizon considered in the analysis. This general assumption can cause biased results when different yearly inflation rates exist for the time horizon of the analysis. Adjustment of the discount rate does not result in the same cost-effectiveness value as the general economic approach where the inflation rate and the non-adjusted discount rate are taken into account. In our manuscript the adjusted-discount rate approach is compared with the general economic approach, where inflation rate and unadjusted discount rates are employed. Furthermore the potential for bias when assuming constant and equal inflation rates for each year is compared with a flexible inflation rate approach. Comparisons of these methods are explored theoretically and then applied to a hypothetical cohort of patients with myocardial infarction.

Essays two to four are all analysis run with caregivers having children suffering from asthma. Nearly 5 million children in the United States are affected by asthma, which is more than 5 percent of the population younger than 18 years. There are several effective drugs that relieve the symptoms of asthma and others are currently being developed but even when these medications are prescribed, they may be underutilized because parents fear the possibility of adverse events. Up to now there is no knowledge, which are the main drivers of caregiver's preferences for a safe and effective medication for pre-school children in general. For this reason a preference study using a conjoint analysis was set up. From these results willingness-to.-pay analyses were also conducted to separate the charcteristics for which caregivers are mostly willing to pay. The overall result was that the most important feature for an asthma treatment, in this study, was the attribute episode free days. The purpose of essay four was to evaluate, using conjoint analysis and utility rating scale from 0 to 10 separately, asthma patients' preferences for different aspects of asthma treatment and the possible existence of learning effects. The respondents were asked, after they decided which treatment options they have chosen, how they would rate the importance (in terms of utility) of their decision. It turns out that

the influence of the product attributes on the score rating was statistically not significant. Even in the three scenarios where it could be shown that the attributes have a statistically significant influence two of the four attributes showed collinearity between each other. Findings of the correlation analyzes could be interpreted as a learning effect between the utility score and the scenario decisions made before.

The final essay was conducted to contribute to current discussions about budget impact modeling. For this two different approaches for the impact of a new pharmaceutical product were analyzed: firstly considering the impact on annual health care expenditures only and secondly additional inclusion of lost insurance premiums due to possible early retirement in patients with chronic diseases. The budget impact was calculated from two different perspectives: a) the impact on health care expenditures and b) on expenditures as well as on health insurance revenues due to premiums. Results in terms of reimbursement decisions of the budget impact analysis varied depending on the assumptions made for the insurance premiums, costs and early retirement rate.

Note that Rito Bergemann co-authored chapter 3 and Peter Zweifel co-authored chapter 5. Chapters 3 and 6 are under review with the Journal of Medical Decision Making. Chapter 5 was accepted for publication in the Journal of Therapeutics and Clinical Risk Management as well as chapter 4. Finally chapter 7 is under review for publication in the Journal of Vascular Health and Risk Management.

Stefan Walzer

Lörrach, November 2006

Chapter 3: Cost-effectiveness: Biased results among current analyses?

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[*] This article has been submitted to the journal of Medical Decision Making.

Abstract

Background: In cost-effectiveness analyses consensus exists among health economists regarding adjustment of discount rates with a constant and equal inflation rate for the time horizon considered in the analysis. This general assumption can cause biased results when different yearly inflation rates exist for the time horizon of the analysis. Adjustment of the discount rate does not result in the same cost-effectiveness value as the general economic approach where the inflation rate and the non-adjusted discount rate are taken into account.

Methods: The adjusted-discount rate approach is compared with the general economic approach, where inflation rate and unadjusted discount rates are employed. Furthermore the potential for bias with assuming constant and equal inflation rates for each year is compared with a varied inflation rate approach. Comparisons of these methods are explored and then applied to a hypothetical cohort of patients with myocardial infarction. The accepted, current cost-effectiveness analyses, which are not taking yearly varying inflation rates into account, produce biased results. This finding is proved by mathematical derivation. Additionally it is shown that the cost differences between the current approach and the suggested approach (including yearly-varying inflation rates) could add up to approximately 30% of total costs incurred during time horizon of 10 years for a hypothetical comparison.

Conclusions: When conducting cost-effectiveness analysis in chronic diseases, unadjusted discount rates, including not constant inflation rates should be employed given the extended time horizon. Due to the fact that inflation rates are difficult to forecast, past values are recommended as potential estimators.

Introduction

The importance of economic evaluations in health technology assessments and submission processes for new pharmaceutical products is continually increasing worldwide. Cost-effectiveness analyses, for example, are essential for the National Institute for Clinical Excellence (NICE) in the United Kingdom submission process (1). NICE evaluates and update their guidelines regularly according to new knowledge and methods which reflects the more current analyses and methodological techniques. Other health authorities, including CCOHTA in Canada (2), PBAC in Australia (3) and others (4-7), also strongly recommend the use of economic evaluations (cost-effectiveness, cost-utility, cost-benefit and net-health-benefit analyses) in their submission guidelines.

Guidelines for economic evaluations have been published and updated in recent years to enable the comparability of different published studies (1,2,8,9).

Health economists generally adjust the discount rate by the yearly inflation rate and assume constant and equal yearly inflation rates (10). However, in the real-world, the inflation rate of health care costs can vary in time, as can be seen in figure 1, where the CPI of the US Medical Services is shown (9). This issue is of paramount importance in health care systems that enforce stringent costs and price controls.

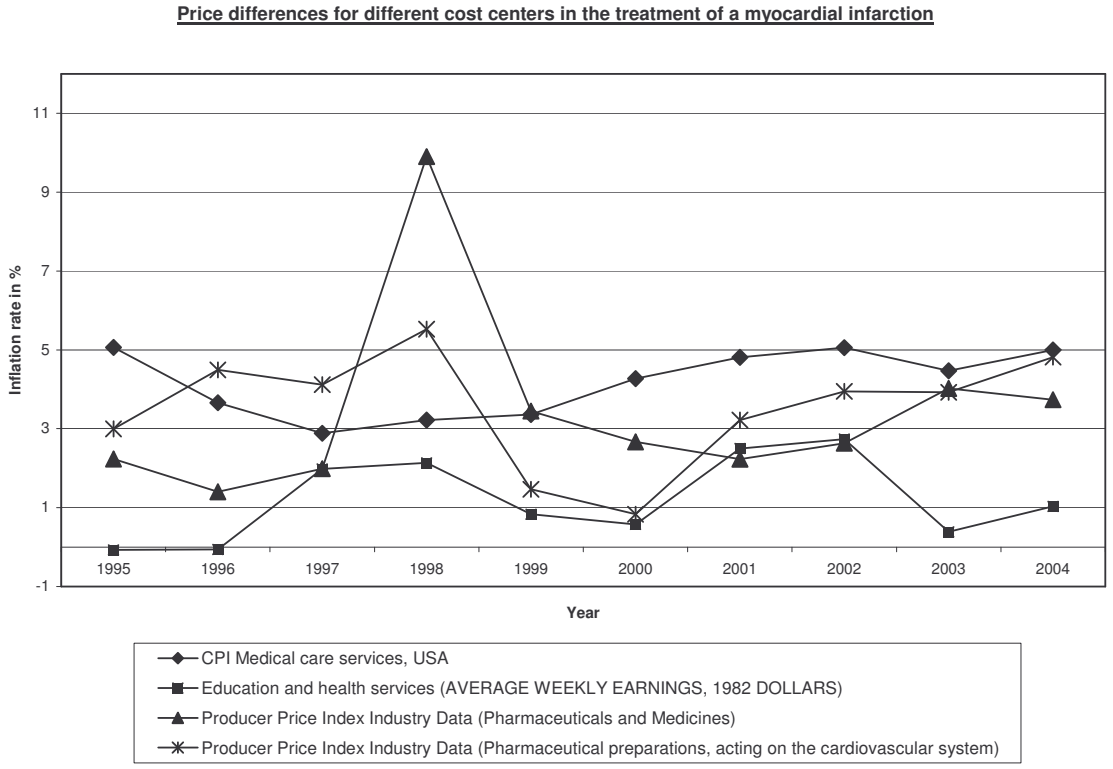

Figure 1 Price changes for different cost centers related to the treatment of a myocardial infarction (9)

According to general economic theory, future costs and effects are calculated to include the increase in these values and the corresponding unadjusted discount rate (11). Reasons for the economic discounting are the myopia of the subjects, which reflects the expectations of future cost increases (i.e. inflation rate) and the preference of the present to the future (12). This behaviour just reflects the risk aversion of subjects for uncertainty.

Current economic evaluations typically adjust the discount rate with a constant and equal yearly inflation rate for both costs and effects (1,10). In diseases with short-term outcomes (e.g. influenza), this approach is valid given the brief time horizon; however for chronic diseases like diabetes, where even a lifetime view could be taken, constant yearly inflation rates are not a reflection of reality.

The present paper explores the difference in results by comparing the current cost-effectiveness approach and an unadjusted discount rate and the yearly inflation rate approach. Furthermore,

the influence of varying yearly inflation rates on cost-effectiveness results is analyzed. Finally, a hypothetical example is given to present recommendations for health economists in the future.

Methods

Cost-effectiveness – Theoretical approach

A cost-effectiveness analysis compares the mean cost-effectiveness of a new health care intervention with the mean cost-effectiveness of an old intervention (12). The analysis is based on the accumulation of costs (either direct or indirect and measured in the given currency) and effects (measured in this example as quality-adjusted life years, QALYs).

Let

C_j = Mean total costs of treatment j

E_j = Mean total effects of treatment j

d = Yearly discount rate; $0 < d < 1$

i_n = Yearly varying inflation rate; $0 < i_n < 1$

i_c = Constant and equal yearly inflation rate; $0 < i_c < 1$

r = Yearly discount rate, where the constant and equal yearly inflation rate i_c was subtracted ($d-i_c = r < d$)

n = time horizon; n=1, … , N

j = A if new treatment

= B if old treatment

The currently used incremental cost-effectiveness ratio approach ($ICER_d$) can then be written as the following (eq 1):

(eq 1)
$$ICER_d = \frac{\sum_{n=1}^{N} \frac{1}{(1+r)^n} (C_a - C_b)_n}{\sum_{n=1}^{N} (E_a - E_b)_n}$$

The effects for treatments A, E_{ad}, and B, E_{bd}, (i.e. $E_{ad} \neq E_{bd}$) are different. Whereas the two different effects are assumed to be the same for both approaches, i.e. that $E_{ad} = E_{ay}$ and $E_{bd} = E_{by}$. Given this assumption, the effects need not be discounted since results would remain equivalent. Additionally health economists have agreed not to inflate effects, which will not be done in this analysis either (12,13).

When assuming a yearly inflation rate in for a cost-effectiveness analysis, equation (eq 1) can be rewritten as follows:

(eq 2)
$$ICER_y = \frac{\sum_{n=1}^{N} \frac{(1+i_n)^n}{(1+d)^n}(C_a - C_b)_n}{\sum_{n=1}^{N}(E_a - E_b)_n}$$

For the first scenario it is assumed that the yearly inflation rates are constant and equal over time, i.e. that $i_n = i_c$. Obviously the incremental cost-effectiveness including the yearly inflation rate should be different in comparison to the cost-effectiveness approach, which adjusts the discount rate with a constant and equal inflation rate. This statement will be proved by assuming the same effects and hence also the same event rates for the two treatment arms A and B for the two approaches (eq 3).

(eq 3)
$$ICER_y \neq ICER_d$$
$$\frac{\sum_{n=1}^{N} \frac{(1+i_n)^n}{(1+d)^n}(C_a - C_b)_n}{\sum_{n=1}^{N}(E_a - E_b)_n} \neq \frac{\sum_{n=1}^{N} \frac{1}{(1+r)^n}(C_a - C_b)_n}{\sum_{n=1}^{N}(E_a - E_b)_n}$$

The left side of the equation is the cost-effectiveness including the yearly inflation rates ($ICER_y$) and the right side is the cost-effectiveness approach adjusting the discount rate for the inflation rate ($ICER_d$). By assuming that the adjusted discount rate r is the difference between the nominal discount rate d (including time preferences) and the expected inflation rates i_c equation (eq 3) is reformulated as:

(eq 4)
$$\frac{\sum_{n=1}^{N} \frac{(1+i_n)^n}{(1+d)^n}(C_a - C_b)_n}{\sum_{n=1}^{N}(E_a - E_b)_n} \neq \frac{\sum_{n=1}^{N} \frac{1}{(1+d-i_c)^n}(C_a - C_b)_n}{\sum_{n=1}^{N}(E_a - E_b)_n}$$

To simplify the comparison equation (eq 4) is first multiplied with the effects and then with the remaining denominator of the right-hand side. Additionally i_n and i_c are set to i_c due to the fact that $i_n = i_c$.

(eq 5)
$$\sum_{n=1}^{N} \frac{1}{(1+d)^n} (1+i_c)^n (1+d-i_c)^n (C_a - C_b)_n \neq \sum_{n=1}^{N} (C_a - C_b)_n$$

After calculations equation (eq 5) results in equation (eq 6):

(eq 6)
$$\sum_{n=1}^{N} \left(\frac{1+d+di_c - i_c^2}{1+d} \right)^n (C_a - C_b)_n \neq \sum_{n=1}^{N} (C_a - C_b)_n$$

When using the Taylor series the following expression can be computed (Appendix 1):

(eq 7)
$$(C_a - C_b)_1 + \sum_{n=1}^{N} \frac{n \cdot \prod_{n=1}^{N} (n-(n+1))}{n!} \cdot x_c^n \cdot (C_a - C_b)_n \neq \sum_{n=1}^{N} (C_a - C_b)_n$$

with x_c being $\left(\frac{1+d+di_c - i_c^2}{1+d} \right)$.

Hence the difference between the current approach and the unadjusted discounted approach is

(eq 8)
$$(C_a - C_b)_1 + \sum_{n=1}^{N} \frac{n \cdot \prod_{n=1}^{N} (n-(n+1))}{n!} \cdot x^n \cdot (C_a - C_b)_n - \sum_{n=1}^{N} (C_a - C_b)_n \neq 0$$

As previously discussed, in the real-world setting, yearly inflation rates vary; therefore equation (eq 4) is re-expressed as follows:

(eq 9) $$\sum_{n=1}^{N} \frac{(1+i_n)^n (1+d-i_c)^n}{(1+d)^n} (C_a - C_b)_n \neq \sum_{n=1}^{N} (C_a - C_b)_n$$

Via the Taylor series (Appendix 2), the following is the difference between the two approaches (eq 10):

(eq 10) $$(C_a - C_b)_1 + \sum_{n=1}^{N} \frac{n \cdot \prod_{n=1}^{N} (n-(n+1))}{n!} \cdot x_y^n \cdot (C_a - C_b)_n \neq \sum_{n=1}^{N} (C_a - C_b)_n$$

with x_y being $\left(\frac{1+d+i_c+i_n+di_n-i_n i_c}{1+d} \right)$.

Equations (eq 8) and (eq 10) prove that the cost-effectiveness ratio is not the same as the current approach for nearly all circumstances when the yearly inflation rate, whether constant or not, is included. The current approach leads to the same results as the approach suggested here in the following situations:

- Costs for treatment A (C_a) are equal to costs of treatment B (C_b)
- The statement ($1+d+di_c-i_c^2$) and ($1+d+i_c+i_n+di_n-i_ni_c$) is equal to zero, which means that the discount rate arguments and the inflation rate arguments are equal to each other, hence the discount rate is not taking the uncertainty into account
- The time horizon n tends towards zero (which is not defined in the cost-effectiveness analysis)

Cost effectiveness – Case example

In order to compare the inflated cost-effectiveness approach with the accepted approach the hypothetical event rates for a myocardial infarction are assumed.

The non-cumulative, hypothetical number of events is taken per 1,000 patients at baseline. These events were assumed to occur in a patient with progressive disease (e.g. type 2 diabetes). Treatment costs for the “old” treatment B was assumed to be 40 US dollars per year,

whereas the “new” and innovative treatment A costs 80 US dollars per year. The cost of a (non-fatal) myocardial infarction was 8,876 US dollars. Cost data for the event was derived from a cost utility analysis in the UK (14), whereas the UK costs were recalculated in US dollars with an exchange rate of 1.8. Utilities were derived from US literature and are as follows (15): Baseline utility at the beginning of the study was 0.689. The disutility for (non-fatal) myocardial infarction was –0.052. The discount rate for both approaches was assumed to be 6%, which includes the expected inflation rate and the myopia of the population. The assumption that the discount rate is constant over time is due to the fact that the population’s myopia will not rapidly fluctuate and inflation is assumed to be relatively stable in the long term (16). As for the theoretical approach, only the costs are inflated and hence also discounted. The effects (quality-adjusted life-years, QALYs) are not discounted and also not inflated because the incremental effects for both approaches are assumed to be equal.

The cumulative QALYs for treatment A after 10 years of treatment according to the assumed event rates (see table 1) are 65.02 for myocardial infarction. The cumulative QALYs for treatment B after 10 years of treatment are therefore 64.94.

Table 1 Event rates for two hypothetical treatments: “Old” treatment A vs “new” treatment B

Non-Cumulative number of myocardial infarction	Years									
	1	2	3	4	5	6	7	8	9	10
("Old") treatment B	2.6	3.8	4.4	5.5	7.3	7.2	8.5	11.5	11.1	14.2
("New") treatment A	2.6	3.6	4.4	5.3	7.2	7.2	8.3	11.2	11.1	13.8

Hypothetical case example to include constant yearly inflation rates

The cost-effectiveness results are reported in table 2 (accepted cost-effectiveness approach without yearly inflation compared to results including inflation). The incremental cost-effectiveness ratios (ICERs) were calculated after 10 years for the comparison of the “old” treatment B versus the “new” treatment A. Effects were the QALYs for the whole patient cohort, which was assumed to be 1,000 patients for each treatment arm at baseline.

Table 2 Comparison of cost-effectiveness approaches after 10 years of hypothetical treatment: Current approach (eq 1) vs "yearly inflation" approach with constant yearly inflation rates (eq 2)

Myocardial infarction	Costs		Effects		Incre-mental costs	Incre-mental effects	ICER
	B	A	B	A	A-B	A-B	
Current cost-effectiveness approach (without yearly inflation rates): Eq 1	626,311	633,500	64.94	65.02	7,189	0.073	98,745
Cost-effectiveness approach including yearly inflation rate: Eq 2	735,578	739,167	64.94	65.02	3,590	0.073	49,309

With the current approach the incremental cost-effectiveness ratio ($ICER_d$, eq1) calculates a cost-effectiveness value of 98,745 US dollars for the event myocardial infarction (table 2). The high ICER (Incremental Cost Effectiveness Ratio) value was to be expected, due to the fact that the differences in the QALYs were marginal but the differences in the costs of complications were high. The inflation approach ($ICER_y$, eq 2) results in a cost-effectiveness value of 49,309 US dollars (table 2), which is within the cost-acceptability threshold of 55,000 US dollars (NICE threshold: approximately 25 - 35,000 pounds (17)). Note that the "new" treatment A is now more cost-effective in comparison to the "old" treatment B.

Assuming a yearly inflation rate of 3% for health care expenditures (including pharmaceutical drugs) and a discount rate of 6%, the costs were underestimated by 17% after 10 years when comparing the accepted cost-effectiveness approach with the approach we suggest (Table 3). The difference in cost-effectiveness increases proportionally, as per equation (eq 7). For myocardial infarction the cost differences between including and excluding yearly inflation result in 105,668 US dollars, or 17% of the overall costs incurred over 10 years. Therefore, the cost difference for the "new" treatment A is approximately 15% of the cumulative costs after 10 years.

Table 3 Cumulative costs of illness for the hypothetical treatments A ("new") and B ("old") treatments for the event myocardial infarction. Comparison between the current approach (eq 1) and the unadjusted discount approach with a constant yearly inflation rate (eq 2). Costs of illness are compared for the two approaches with and without the yearly inflation rate (eq 8).

Myocardial infarction Year	"Old" treatment B without inflation (eq 1)	"New" treatment A without inflation (eq 1)	"Old" treatment B including inflation (eq 2)	"New" treatment A including inflation (eq 2)	Difference between "old" treatments with and without inflation (eq 8)	Difference between "new" treatments with and without inflation (eq 8)
1	22,444	22,483	22,463	32,058	19	9,575
2	52,601	52,678	54,348	62,305	1,746	9,627
3	89,450	89,564	92,368	100,357	2,918	10,793
4	135,502	133,977	141,309	147,560	5,807	13,583
5	195,775	194,285	208,202	213,579	12,427	19,294
6	256,047	254,590	276,159	281,578	20,112	26,988
7	325,521	324,097	358,785	362,304	33,264	38,207
8	421,767	417,865	473,910	474,473	52,143	56,608
9	514,666	510,794	588,367	588,976	73,701	78,181
10	633,500	626,311	739,167	735,578	105,668	109,267

Hypothetical case example to include varying yearly inflation rates

The cost-effectiveness results for the approach including yearly varying inflation rates are shown in table 5. The assumptions for the analysis were the same as described above aside from the inflation rate variation in the first column of table 6. The costs could thereby be composed of pharmaceutical costs and their inflation rate (or even deflation rate, e.g. due to a reduction in costs in accordance with a particular health care policy), costs for the human resources (e.g. physician and nurses and their salary increases) and the costs for medical devices and their respective inflation rate. For this hypothetical analysis it is assumed that the weighted average of all cost increases is taken into account. This means that the different yearly variations in the inflation rate for the various categories, which are relevant for the treatment of a disease like myocardial infarction, are assumed to be known. For the base case analysis it is assumed that the varying inflation rates, for the above-mentioned categories, are the same for each category assuming the numbers of the CPI Medical Care services (9).

Table 4 Cost-effectiveness approaches in comparison after 10 years of hypothetical treatment: Current approach (eq 1) vs "yearly inflation" approach with varying yearly inflation rates (eq 2)

Myocardial infarction	Costs		Effects		Incre-mental costs	Incre-mental effects	ICER
	B	A	B	A	A-B	A-B	
Current cost-effectiveness approach (without yearly inflation rates): Eq 1	626,311	633,500	64.94	65.02	7,189	0.073	98,745
Cost-effectiveness approach including yearly inflation rates: Eq 2	819,453	824,755	64.94	65.02	5,303	0.073	72,837

The results of the current approach for the incremental cost-effectiveness ratios (ICER) are the same as in the above analysis. The inflation approach including varying inflation rates per year results in a cost-effectiveness value of 72,837 US dollars for myocardial infarction which is now higher than without the inclusion of a yearly varying inflation rate. When considering a cost-acceptability threshold of 55,000 US dollars per QALY the new treatment A would likely not be accepted by health authorities.

The cost differences between the current approach without including the yearly inflation rate and the yearly varying inflation rate approach add up to 191,255 US dollars, which is approximately 30% of the total costs incurred during the time horizon of 10 years. The cost difference for the "new" treatment A is about 23% of the cumulative costs after 10 years (table 4).

Table 5 Cumulative costs of illness for the hypothetical treatments A ("new") and B ("old") treatments for the event myocardial infarction. Comparison between the current approach (eq 1) and the yearly varying inflation approach (eq 2). Costs of illness are compared for the two approaches with and without the yearly inflation rate (eq 10).

Myocardial infarction Year	"Old" treatment B without inflation (eq 1)	"New" treatment A without inflation (eq 1)	"Old" treatment B including inflation (eq 2)	"New" treatment A including inflation (eq 2)	Difference between "old" treatments with and without inflation (eq 10)	Difference between "new" treatments with and without inflation (eq 10)
1	22,444	22,483	22,913	32,470	469	9,986
2	52,601	52,678	55,207	63,105	2,605	10,427
3	89,450	89,564	93,100	101,028	3,649	11,465
4	135,502	133,977	142,464	148,642	6,962	14,665
5	195,775	194,285	210,548	215,840	14,773	21,555
6	256,047	254,590	283,704	289,044	27,657	34,453
7	325,521	324,097	377,059	380,253	51,538	56,156

8	421,767	417,865	511,920	511,651	90,152	93,786
9	514,666	510,794	641,976	641,763	127,310	130,969
10	633,500	626,311	824,755	819,453	191,255	193,141

For a more comprehensive analysis, the following inflation rates and weights for the costs were assumed:

In this example, we assume that several cost centers influence the overall costs of the myocardial infarction treatment and hence the price range for this treatment changes over time. The weights for the various cost centers are hypothetical: 60% of the overall costs are dependent on centers other than human resources, pharmaceuticals and medical devices. The weights for medical devices and drugs are assumed to be 10%, respectively, and the weight for human resources (physicians, nurses) is assumed to be 20%. The inflation rates for the groups were derived from official figures from the US Department of Labor, Bureau of Labor Statistics (table 6).

Table 6 Price changes for different cost centers related to the treatment of a myocardial infarction (9)

Year	OTHERS (CPI Medical care services, USA)	HUMAN RESOURCES (Education and health services (AVERAGE WEEKLY EARNINGS, 1982 DOLLARS))	MEDICAL DEVICES (Producer Price Index Industry Data (Pharmaceuticals and Medicines))	PHARMACEUTICALS (Producer Price Index Industry Data (Pharmaceutical preparations, acting on the cardiovascular system))
1995	5.06	-0.07	2.23	3.00
1996	3.66	-0.06	1.40	4.50
1997	2.88	1.98	1.99	4.12
1998	3.22	2.14	9.90	5.53
1999	3.36	0.83	3.45	1.46
2000	4.27	0.57	2.67	0.83
2001	4.81	2.50	2.23	3.22
2002	5.06	2.74	2.63	3.95
2003	4.47	0.39	4.02	3.93
2004	5.00	1.03	3.74	4.81

The results of the current approach for the incremental cost-effectiveness ratios (ICER) are the same as in the above analysis. The inflation approach including varying inflation rates for the various cost centers per year results in a cost-effectiveness value of 65,465 US dollars, which is

now higher than without the inclusion of a yearly varying inflation rate but still lower in comparison to the more stringent assumption of varying inflation rates for the overall costs (table 7). At a cost-acceptability threshold of 55,000 US dollars per QALY, the new treatment A would again probably no longer be accepted.

Table 7 Cost-effectiveness approaches in comparison after 10 years of hypothetical treatment: Current approach (eq 1) vs "yearly inflation" approach with varying yearly inflation rates (eq 2) assuming varying price changes for various cost centers

Myocardial infarction	Costs		Effects		Incre-mental costs	Incre-mental effects	ICER
	B	A	B	A	A-B	A-B	
Current cost-effectiveness approach (without yearly inflation rates): Eq 1	626,311	633,500	64.94	65.02	7,189	0.073	98,745
Cost-effectiveness approach including yearly inflation rates: Eq 2	773,782	778,548	64.94	65.02	4,766	0.073	65,465

The cost differences between the accepted approach without including the yearly inflation rate and the approach we suggest (including yearly varying inflation rates) add up to 145,048 US dollars, or 23% of the total costs incurred over a 10 year time horizon (table 8). The cost difference for the "new" treatment A is 19% of the cumulative costs after 10 years (table 4).

Table 8 Cumulative costs of illness for the hypothetical treatments A ("new") and B ("old") treatments for the event myocardial infarction. Comparison between the current approach (eq 1) and the yearly varying inflation approach (eq 2). Costs of illness are compared for the two approaches with and without the yearly inflation rate (eq 10) assuming varying price changes for various cost centers

Myo-cardial infarction Year	"Old" treatment B without inflation (eq 1)	"New" treatment A without inflation (eq 1)	"Old" treatment B including inflation (eq 2)	"New" treatment A including inflation (eq 2)	Difference between "old" treatments with and without inflation (eq 10)	Difference between "new" treatments with and without inflation (eq 10)
1	22,444	22,483	22,582	31,917	138	9,434
2	52,601	52,678	54,326	62,031	1,725	9,353
3	89,450	89,564	92,056	99,793	2,606	10,229
4	135,502	133,977	142,735	148,671	7,233	14,694
5	195,775	194,285	208,581	213,658	12,806	19,373
6	256,047	254,590	276,650	281,771	20,603	27,180
7	325,521	324,097	364,652	367,749	39,131	43,651

8	421,767	417,865	491,346	491,186	69,579	73,321
9	514,666	510,794	611,477	611,366	96,811	100,571
10	633,500	626,311	778,548	773,782	145,048	147,471

Discussion

Yearly inflation rates can be observed in the health care market of all industrialized countries. Even in countries with a national health care system, as in the United Kingdom or Italy, health care costs increase every year. The analysis presented herein shows that the results of cost-effectiveness analyses may be biased when varying inflation rates are not considered.

Current guidelines for the evaluation of new pharmaceutical products do not take yearly varying inflation rates into account. Furthermore the guidelines only consider the adjusted discount rates, which means that the results are already biased, equations (eq 7) and (eq 9).

Lipscomb et al. (10) recommend adjusting the discount rate with the inflation rate in a chapter of the current gold-standard guideline about cost-effectiveness analysis – Gold et al. But also this recommendation could be biased as the analysis above shows. That biases might also appear in the results related to the current cost-effectiveness approach when comparing them to an approach including a yearly inflation rate.

On the other hand, the guide published by the Panel on Cost-effectiveness in Health and Medicine (18) has recognised the problem of future costs directly related to the disease in question. The authors note the importance of considering increasing costs over time and they admit to methodological problems e.g. by modelling the medical CPI. Since it is difficult to forecast the inflation rate, future research should aim to analyse the possible bias when estimating future inflation rates on the basis of prior precedent. Nonetheless, it is essential to seperate the inflation rate into the part related to higher productivity, e.g. caused by innovations, and the part directly related to the increase of costs. Luce et al. (18) recommend using the yearly inflation rate approach to analyse the correct influence of costs, especially for cost-effectiveness analyses, which are done for chronic diseases with a long time horizon. The above analysis supports the recommendation by the cost-effectiveness panel. It is essential to take the yearly inflation rate into account to prevent the health authorities from using biased cost-effectiveness ratios.

Current guidelines published by health authorities throughout the world (1-7,13) do not explicitly advise health economists on the problem of future health care costs and the related inflation

rate. The NICE guideline (1), for instance, speaks about a sufficient time horizon to reflect the impact on costs and effectiveness, especially for chronic diseases. They also mention the importance of using a discount rate to calculate future costs for the present. Due to the varying inflation rates in the course of time, it would also be important to compare cost-effectiveness analyses for health technology assessments when the yearly inflation rate is included.

In the light of the recommendations by the Washington panel on cost-effectiveness analyses as well as the hypothetical and theoretical results of this study, it is advisable to include the yearly inflation rates for long-term analyses in the economic evaluation separately from the discount rate. Additional estimations for the yearly varying inflation rates should also be taken into account. Further research on real effectiveness and cost data is recommended.

The new investigated method with the inclusion of variable unadjusted discount rates and inflation rates should be used for long-term analysis in Health Economics. The presentation of the results will allow decision makers to get an impression of the influences of the above mentioned uncertainty and how maybe a result based on the old method would lead to a false negative or false positive conclusion in terms of cost-effectiveness or reimbursement.

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Appendix

Appendix 1: Derivation of the Taylor series for the comparison between the current cost-effectiveness approach and a yearly but constant inflation rate approach

(eq 6) $$\sum_{n=1}^{N}\left(\frac{1+d+di_c-i_c^2}{1+d}\right)^n (C_a-C_b)_n \neq \sum_{n=1}^{N}(C_a-C_b)_n$$

which results in

$$(C_a-C_b)+x_c\cdot(C_a-C_b)+\frac{2\cdot(2-1)}{2!}x_c^2\cdot(C_a-C_b)+\frac{3\cdot(3-1)\cdot(3-2)}{3!}x_c^3\cdot(C_a-C_b)+\ldots\neq\sum_{n=1}^{N}(C_a-C_b)_n$$

for n>0 and x_c being $\left(\frac{1+d+di_c-i_c^2}{1+d}\right)$.

When using the Taylor series the following expression can then be computed:

(eq 7) $$(C_a-C_b)_1+\sum_{n=1}^{N}\frac{n\cdot\prod_{n=1}^{N}(n-(n+1))}{n!}\cdot x_c^n\cdot(C_a-C_b)_n\neq\sum_{n=1}^{N}(C_a-C_b)_n$$

Appendix 2: Derivation of the Taylor series for the comparison between the current cost-effectiveness approach and a yearly, varying inflation rate approach

(eq 9) $$\sum_{n=1}^{N}\frac{(1+i_n)^n(1+d-i_c)^n}{(1+d)^n}(C_a-C_b)_n\neq\sum_{n=1}^{N}(C_a-C_b)_n$$

which results in

$$(C_a-C_b)+x_y\cdot(C_a-C_b)+\frac{2\cdot(2-1)}{2!}x_y^2\cdot(C_a-C_b)+\frac{3\cdot(3-1)\cdot(3-2)}{3!}x_y^3\cdot(C_a-C_b)+\ldots\neq\sum_{n=1}^{N}(C_a-C_b)_n$$

for n>0 and x_y being $\left(\frac{1+d+i_c+i_n+di_n-i_ni_c}{1+d}\right)$.

When using the Taylor series the following expression can then be computed:

(eq 10)
$$\left(C_a - C_b\right)_1 + \sum_{n=1}^{N} \frac{n \cdot \prod_{n=1}^{N} \left(n - (n+1)\right)}{n!} \cdot x_y^n \cdot \left(C_a - C_b\right)_n \neq \sum_{n=1}^{N} \left(C_a - C_b\right)_n$$

Chapter 4: What do parents want from their child's asthma treatment?

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Abstract

Background: Nearly 5 million children in the United States are affected by asthma, which is more than 5 percent of the population younger than 18 years. In children four years or younger, the prevalence increased 160 percent from 1980 to 1994. There are several effective drugs that relieve the symptoms of asthma and others are currently being developed but even when these medications are prescribed, they may be underutilized because parents fear the possibility of adverse events. Up to now there is no knowledge which are the main drivers of caregiver's preferences for a safe and effective medication for pre-school children in general. The study population were caregivers with children aged 4 years or below. Sample size was 42, results were checked by Monte-Carlo simulation.

Material and Methods: For a conjoint analysis a status quo treatment and hypothetical treatment options were defined by four attributes: Episode free days, risk of exacerbation, information available for the long-term impact of the treatment and out-of-pocket expenses. It was possible to use the status quo as the reference scenario, permitting to couch this ranking in terms of a decision to purchase the product. Relative importance for each product attribute as well as utility estimations for each attribute level were calculated.

Results and Discussion: The overall result was that the most important feature for an asthma treatment, in this study, was the attribute episode free days. On a scale from 0 to 100 this attribute got the calculated relative importance of 44.2. In contrast to this finding is the relative importance of the attribute EXACERBATION, which only reached 16.2, which is the most unimportant attribute of the attributes offered. Even the variable INFORMATION available on long-term effects in children between 4 years and 14 years of age was more important than the side effects (19.2). Out-of-pocket expenses per month were the second most (relative) important attribute (20.5).

Introduction

Asthma is a chronic disease that effects between 9 and 12 million persons in the United States [1] and is the most common chronic disease of childhood [2]. Nearly 5 million children in the United States are affected by asthma, which is more than 5 percent of the population younger than 18 years [3]. It is the leading cause of lost school days in children [4, 5]. In children four years or younger, the prevalence increased 160 percent from 1980 to 1994. To avoid the missing school days pre-school children should be treated in the most effective way as possible. There are several effective drugs that relieve the symptoms of asthma and others are currently being developed but even when these medications are prescribed, they may be underutilized because parents fear the possibility of adverse events and long-term effects. Up to now there is no knowledge which are the main drivers of caregiver's preferences for a safe and effective medication for pre-school children in general.

Asthma or wheezing conditions was not explicitly defined. Respondents were screened based on the asthma medication that the child is currently taking for the treatment of the condition. Severity of asthma / wheezing condition was identified by applying the "Evaluation of a short form for measuring health-related quality of life among pediatric asthma patients".

For an economic evaluation (such as a preference study) of treatments in diseases such as asthma, where a substantial impact is on quality of life rather than survival, it is crucial to be able to incorporate the effects of the new therapies on quality of life and include those effects in the economic evaluation. Within health care there is substantial evidence to suggest that, in addition to the treatment outcome (that is, the effectiveness), other aspects of the process of receiving treatment are also important for individuals [6, 7, 8, 9]. Conjoint analysis was originally developed for market research into consumer preferences, and is a method that investigates the relative importance of groups of attributes, e.g., products with certain properties or more abstract concepts such as treatment procedures [10, 11]. It has been applied to various aspects of health care; for reviews, see Ryan 1996 [12] or Szeinbach et al. 1999 [13]. The method can thus be used to analyze patient preferences for various treatment alternatives.

No asthma treatment regimen is likely to have all the attributes that patients would ideally like; for example, a regimen might be highly effective (desirable) but expensive (undesirable). Conjoint analysis provides a method of “trading off” desirable attributes against undesirable ones, and assessing which attributes are most important in determining the patient preferences for one regimen over another. The target population of this study is pre-school children with a maximum age of 4 years. Obviously the possibility to ask the children themselves was naturally limited and hence the caregivers answered for them.

The purpose of this study was to evaluate, using conjoint analysis, asthma patients’ preferences for different aspects of asthma treatment, including efficacy (episode free days), side effects (risk of exacerbation), available information by the FDA about long-term effects, and out-of-pocket expenses. The relative importance was evaluated for each of the described attributes.

Materials and Methods

The methods used for the discrete choice part of this study were already explained in a recent paper [14]. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by local ethics committees, and all participants gave written informed consent.

It is assumed that the preferences of caregivers of pre-school children with asthma could be taken as approximations for the utility of their child for a given treatment. If the caregiver is a pure altruist with respect to the child, i.e. cares but respects the child's preferences, the caretaker's responses will reflect the child's preferences. For the present analysis caregivers were asked to choose between two hypothetical asthma treatments for their child. The decision was based on a status quo treatment versus a new (hypothetical) treatment with changed attribute levels. Possible attributes and their levels were tested in various face-to-face interviews with caregivers in autumn 2005. Potential and actual study participants were contacted based on information from a consumer database in the United States. The tested attributes were ease of handling, efficacy (episode free days), time for administration, number of administrations per day, side effects (risk of asthmatic exacerbation), available information by the FDA (information on long-term effects in children between 4 and 14 years of age) as well as expenses. This pre-test was deducted mainly as qualitative interviews with seven applicants (see table 1). It turned out that the main attributes for the treatment of asthma were expenses, episode free days, side effects and available information by the FDA.

Table 1: Product attributes and levels retained in the main survey

Attributes	Label	Levels	Value labels
Episode free days	FREEDAYS	Increase from 180 to 200 episode free days per year	200
		Increase from 180 to 220 episode free days per year	220
		Decrease from 180 to 1600 episode free days per year	180
		Decrease from 180 to 140 episode free days per year	140
Exacerbation	EXACERBATION	Risk of EXACERBATION: 6% of patients develop a mild to severe EXACERBATION	6

		Risk of EXACERBATION: 10% of patients develop a mild to severe EXACERBATION	10
		Risk of EXACERBATION: 16% of patients develop a mild to severe EXACERBATION	16
Information about long-term effects by the FDA available	INFORMATION	INFORMATION available on long-term effects in children between 4 years and 14 years of age	1
		No INFORMATION available on long-term effects in children between 4 years and 14 years of age	2
Out-of-pocket EXPENSES	EXPENSES	$10 per month	10
		$30 per month	30
		$50 per month	50

Pre-test interviews resulted in the fact that the main attributes for the treatment of asthma were expenses, episode free days, side effects and available information by the FDA [(14)].

In conjoint analysis, several attributes of treatment are selected and a range of possible values ("levels") are defined for each attribute. These are used to create a number of treatment concepts, each with different levels for the various attributes. The levels of attributes were defined as follows (see table 1): 'Episode free days' (FREEDAYS), symbolizing the change in the risk to develop asthma attacks from an unknown individual level, takes on changes from 180 days (baseline [15]) to 200 and 220 days per year as well as a possible decrease in change to 160 and 140 days per year. 'Exacerbation' (EXACERBATION), defined as developing mild or moderate exacerbation, varies between levels of 6%, 10% and 16%. A recent study with adults has shown that mild to moderate asthmatic patients are very much affected by their disease and patient's utility was decreasing when developing an exacerbation [16]. It is assumed that these findings are also valid in pre-school children. For the FDA 'information' on long-term effects (INFORMATION) in children between 4 and 14 years of age two levels were used: Availability or non availability. Other studies have shown that caregivers could be concerned about the missing long-term effects of asthma treatment in pre-school children [17]. The 'out-of-pocket cost' (EXPENSES) per month ranges from $10, $30 to $50. Status quo treatment (see table 2) was defined as having 180 episode free days per year and a risk to develop a mild or severe

exacerbation of 10%. Information by the FDA is available and the monthly out-of-pocket expenses are $20.

Table 2: Status quo treatment – definition by attribute levels

Attributes	Levels
Episode free days	180 episode free days per year
EXACERBATION	Risk of EXACERBATION: 10% of patients develop a mild to severe EXACERBATION
INFORMATION availability	INFORMATION available on long-term effects in children between 4 years and 14 years of age
Out-of-pocket EXPENSES	$20 per month

Since the second and the last attributes have 3 levels each, while FREEDAYS has 4 and INFORMATION has two, the number of scenarios amounts to a total of 72 (= 4*3*2*3). Techniques have been developed to reduce the number of possible scenarios while still being able to infer utilities for all combinations of levels of the attributes [18]. Using the ORTHOPLAN procedure, which implicitly assumes a linear utility function, programmed in the software package SPSS, the design was reduced to 16 scenarios. All study participants had to answer these 16 variants as well as two hold-out cards whereas the scenarios were randomly assigned to take care of a possible question ordering bias [19]. With regard to each variant, respondents had to indicate whether or not they would choose the treatment and would pay the monthly out-of-pocket expenses (for a sample card presented to study participants, see Appendix A.1).

Results

Descriptive statistics

In table 3, descriptive statistics of the caregivers with regard to the dependent and explanatory variables are reported. Nearly all caregivers who took part in the survey were female (92.9%). The average of the respondents have one child. Caregivers were also asked how confident they are in knowing what they do when they are thinking about their overall ability to take care of their family's general health – eating right, getting check-ups, taking medicine, deciding when to see the doctor. Within the whole population 42.9% agreed with the statement feeling "Very confident" and another 26.7% agreed with the statement feeling "Extremely confident". Summarized 31% felt fairly and/or somewhat confident and 69% of caregivers felt very and/or extremely confident.

In 18% of the cases the doctor never told the caregiver the asthma severity diagnosis of their child. Anyway, 21.4% of caregivers rated the severity of their child as very mild, whereas no physician diagnosed a child with that rate. Also differences in diagnosing severe asthma could be detected: 4.8% of physicians diagnosed children as having severe asthma whereas only 2.4% of caregivers diagnosed so.

Table 3: Descriptive Statistics of caregivers

	Percent	Cumulative Percentage
Gender		
Female	92.9	
Age		
<30 years	28.6	
30 – 39 years	42.8	71.4
40 – 49 years	19.1	90.5
>50 years	9.5	100
Number of children ≤ 4 years		
1 child	73.8	
2 children	26.2	100
Rating of health care		
Fairly/somewhat confident	31.0	
Very/extremely confident	69.0	100
Number of children with diagnosed asthma and/or wheezing conditions		
1 child	73.8	
2 children	26.2	100
Relationship to children		
Mother or female guardian	85.7	

Father or male guardian	7.1	92.9
Grandparent	7.1	100
Level of education		
High school graduate (or lower)	11.9	
Some college	31.0	42.9
Associate / Bachelor's degree	40.5	83.3
Postgraduate school	14.3	97.6*
Current employment situation		
Working full-time	40.5	
Working part-time	11.9	52.4
Homemaker	45.2	97.6**
Annual household income in 2004		
< US$25,000	4.8	
US$ 25,000 – 49,999	45.2	50.0
US$ 50,000 – 74,999	19.0	69.0
> US$ 75,000	23.8	92.9***
Smoking		
Smoker	28.6	
Non-Smoker	71.4	
Severity estimation by caregiver		
Very mild	21.4	
Mild	35.7	57.1
Moderate	40.5	97.6
Severe	2.4	100
Severity diagnosis by physician		
Mild	35.7	
Moderate	40.5	76.2
Severe	4.8	81.0
Doctor never told me the severity	19.9	100
Compliance estimation for other caregivers		
< 20%	54.8	
20% - 39%	23.8	78.6
40% - 59%	7.1	85.7
> 60%	14.3	100
Own compliance estimation		
< 10%	76.2	
10% - 19%	11.9	88.1
20% - 29%	4.8	92.9
> 30%	7.1	100
Children characteristics	**Percent**	**Cumulative Percent**
Age		
≤ 2 years (child 1)	33.3	
≤ 2 years (child 2)	0	

Gender		
Female (child 1)	35.7	
Female (child 2)	66.7	
Race		
White	88.1	
Black	4.8	92.9
Other	7.1	100
Medications currently taken (more than one drug could be chosen)		
Accolate	2.4	
Advair	2.4	
Flovent	7.1	
Pulmicort Respules	28.6	
Singulair	76.2	
Prevalence of asthma	88.1	
Prevalence of wheezing conditions	26.2	
Prevalence of allergies	71.4	--
Cough in last 4 weeks		
Never	14.3	
A few days	31.0	45.3
Some days	23.8	69.1
Most days	19.0	88.1
Every day	11.9	100
Wheezing conditions in last 4 weeks		
Never	26.2	
A few days	33.3	59.5
Some days	35.7	95.1
Every day	2.4	97.6****
Shortness of breath in last 4 weeks		
Never	57.1	
A few days	16.7	73.8
Some days	19.0	92.8
Most of the days	4.8	97.6****
Asthma attacks in last 4 weeks		
Never	85.7	
A few days	9.5	95.2
Some days	2.4	97.6
Most of the days	2.4	100
Number of asthma attacks in last 4 weeks		
0	16.7	
1 attack	50.0	66.7
2 attacks	16.7	83.3
6 attacks	16.7	100

Awakened in last 4 weeks due to asthma/wheezing conditions		
Never	38.1	
A few days	40.5	78.6
Some days	16.7	95.2
Most of the days	4.8	100

* Other education: 2.4%; ** Retired: 2.4%; *** Declined to answer: 7.1%;

**** Don' know: 2.4%

Caregivers were also asked about their estimation of how many caregivers (in general) forget to provide the asthma medication for their child during a week due to several reasons (job stress, care for other children, etc.) in one week on average. In various studies it turned out that up to 95% of caregivers (on average around 50%) don't give the medication in the right way (not regularly, wrong dosage, etc.) [26, 27]. Study respondents estimated that 16.7% of other caregivers never forget this per week. 54.8% estimated that a maximum of 19% forget the medication of their child. But when asking in how many cases the caregivers itself forget it 88.1% say that they forget this themselves at a maximum of 19%. When estimating for other caregivers the cumulative 88% is reached for around 69% of caregivers who will forget offering the (correct) treatment, which is nearly the number that could be found in the literature.

The medications children currently taking for the treatment of asthma and/or wheezing conditions are distributed in this sample as follows, whereas more than one drug could be taken for treatment: 76.2% are taking Singulair, 28.6% Pulmicort Respules, 7.1% Flovent and Accolate and Advair are taken each by 2.4. During the last 4 weeks in advance of the survey 23.8% of children have had experienced cough on some days whereas 19% experienced this complication most days. 11.9% of children experienced cough every day. The condition wheezing was less often experienced every day (2.4%) but nearly 33% have experienced wheezing a few days in the last 4 weeks. Caregivers reported that 57.1% of their children never had shortness of breath but also 19% reported that their children experienced that symptom some days in the last month. Asthma attacks in this study population were not that frequent (never experienced in the last 4 weeks: 85.7%) with experiences of this symptom a few days in 9.5%. Anyway of those who experienced asthma attacks 50% had one attack in the last month, 16.7% had two and another 16.7% had six asthma attacks. The possibility of awaken during the

night due to asthma/wheezing conditions, such as asthma attacks, etc., was relatively frequent but not that severe: 38.1% never awakened, 40.5% awakened a few nights, 16.7% some nights but also 4.8% awakened each night.

52.4% of pediatricians of these children offered most or all the time treatment choices to the caregivers (table 4). While they were doing so, the physicians also discussed the pros and cons of the offered/suggested treatments. After discussions with caregivers, they stated that pediatricians take their preferences into account when making treatment decisions for their child's asthma or wheezing conditions care. This could be taken as an indication that these caregivers should be interested in available information by the FDA on long-term effects. Additionally 85.7% of caregivers reported to follow the asthma or wheezing conditions medication schedule given to them by their child's doctor or nurse. On the other hand around 90% mentioned that they provide medications to their child when they feel it was appropriate.

Table 4: Treatment behavior of caregivers

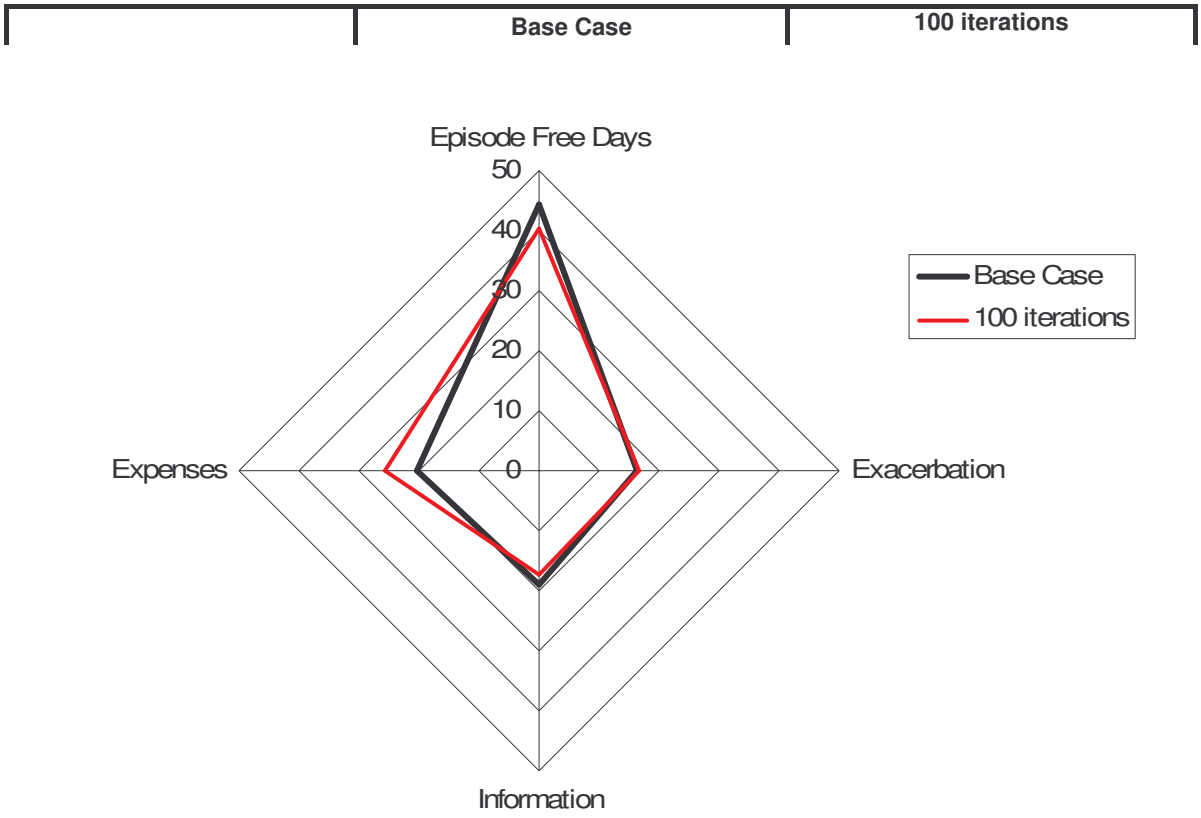
	Percent	Cumulative Percent
Physician offers treatment choices in child's asthma or wheezing conditions care		
All of the time	28.6	
Most of the time	23.8	52.4
Some of the time	28.6	81.0
A little of the time	2.4	83.3
None of the time	16.7	100
Physician discusses the pros and cons of each treatment choice with you		
All of the time	35.7	
Most of the time	33.3	69.0
Some of the time	9.5	78.6
A little of the time	7.1	85.7
None of the time	14.3	100
Physician takes your preferences into account when making treatment decisions for your child		
All of the time	35.7	
Most of the time	40.5	76.2
Some of the time	9.5	85.7
A little of the time	4.8	90.5
None of the time	9.5	100
I follow the asthma or wheezing conditions medication schedule given to me by my child's doctor or nurse		
Yes	85.7	
No	14.3	100
I provide asthma or wheezing conditions medication(s) to my child when I feel is appropriate		
Yes	90.5	
No	9.5	100

Conjoint analysis

Results from the discrete choice decisions served as a basis for a conjoint analysis [11]. Relative importance for each product attribute as well as utility estimations for each attribute level were calculated.

For the caregivers the key attribute for an asthma drug for the treatment of childhood asthma is FREEDAYS. On a scale from 0 to 100 this attribute got the calculated relative importance of 44.2 (see figure 1).

Figure 1: Relative importance of Factors for Treatment of Pediatric Asthma and/or Wheezing Conditions. Base Case based on the real number of respondents in comparison to 100 iterations from a Monte-Carlo simulation



	Base Case	100 iterations
FREEDAYS	44.189	40.303
EXACERBATION	16.181	16.667
INFORMATION	19.153	17.362
EXPENSES	20.477	25.668

In contrast to this finding is the relative importance of the attribute EXACERBATION, which only reached 16.2, which is the most unimportant attribute of the attributes offered. Even the variable INFORMATION available on long-term effects in children between 4 years and 14 years of age was more important than the side effects (19.2). Out-of-pocket expenses per month were the

second most (relative) important attribute, whereas it was only slightly more important than the attribute INFORMATION (20.5).

The utilities for the efficacy attribute (FREEDAYS) are positive for the increase of episode free days and negative for the decrease of episode free days (see table 5). However, the utility is not increasing with the increasing number of episode free days. Anyway with decreasing episode free days the utilities are also decreasing. The utilities for the increasing out-of-pocket EXPENSES were decreasing with the growing costs. Furthermore the utility for the available information is positive and vice versa.

Table 5: Conjoint analysis – Utility estimations (Base Case)

	Utility Estimate	Std. Error
FREEDAYS		
Increase episode free days 180 to 200	.057	.038
Increase episode free days 180 to 220	.039	.038
Decrease episode free days 180 to 160	-.045	.038
Decrease episode free days 180 to 140	-.051	.038
EXACERBATION		
6% develop an EXACERBATION	.036	.027
10% develop an EXACERBATION	.071	.053
16% develop an EXACERBATION	.107	.080
INFORMATION		
INFORMATION available	-.060	.044
No INFORMATION available	-.119	.088
EXPENSES		
$10	-.018	.027
$30	-.037	.053
$50	-.055	.080
(Constant)	.116	.096

The conjoint analysis' findings were also tested for its possibilities to predict the observed values: Pearson's R was relatively good (0.73) as well as Kendall's tau (0.54), whereas both

measures were highly significant for the correlation between the observed and predicted values (see table 6). Furthermore Kendall's tau for the hold-out cards is 1.

Table 6: Conjoint analysis - Correlations between observed and estimated preferences

	Value	Sig.
Pearson's R	.703	.001
Kendall's tau	.543	.002
Kendall's tau for Holdouts	1.000	.

Sensitivity Analysis

Due to budget restrictions, only 42 respondents could be included in this survey. However, to improve the validity and significance of the study the data have also been simulated by 100 Monte-Carlo iterations. Monte-Carlo simulations are reproducing data dependent on the input data and their corresponding distributions. In this way it can be checked how sensitive the underlying base data are to changes in the inputs. For the simulation the binomial distribution was assumed for the simulation of the outcome "Scenario". For the caregiver's socio-economic characteristics a beta-pert distribution was assumed to stay within the calculated ranges of the parameters given by the study participants [20]. It turned out that the ranking for the relative importance of the four attributes is not changed when using 100 iterations (see figure 1), which was used as having 100 respondents. This procedure is state-of-the-art for checking uncertainty around the data in economic evaluation studies [20].

Discussion

This study has investigated patient preferences for different attributes of asthma treatment in pre-school children. The overall result was that the most important feature for an asthma treatment in this study was the episode free days.

The major criticism about the study is the small sample size of 42 respondents. Due to this fact the results could be biased due to outliers who could be overweighed. Within a larger population the results could maybe more smoothed and outliers would not be overweighed as can be assumed in a small sample size. However in a Monte-Carlo simulation study, which was done along that original study using the study data, it turned out that the conjoint results are relatively stable and could give a first impression about preferences for a treatment within such a special population like caregivers of asthmatic children.

The attribute EXACERBATION turned out to be the most unimportant attribute in the base analysis also when comparing with the variable INFORMATION available on long-term effects in children between 4 years and 14 years of age. This finding could maybe be explained that caregivers weight the possible long-term effects, which should be explained by the FDA information, higher than the short-term side effects like the risk of an asthmatic exacerbation. The utilities for each attribute level was in the range as expected with two exceptions: The utility for the efficacy attribute is not increasing with the increasing number of episode free days. One possible explanation for this could be that the caregivers did not believe that the efficacy would increase by nearly 22% (possible theoretical misspecification bias [19]) - from 180 days to 220 days. Anyway with decreasing episode free days the utilities are also decreasing. Counterintuitive is the finding for the utilities of the risk of exacerbations: The higher the probability of an exacerbation, the higher the utility. Maybe the relative low importance of that attribute could lead to that finding, i.e. that the other positive impacts traded the negative impact of this attribute out. Additionally only few children experienced (very) often shortness of breath or much asthma attacks in the last four weeks in advance of the study. Maybe caregivers are less risk averse on this attribute when comparing it to the other three. Of course this could be a major caveat of the study, however the aim of a discrete choice analysis is to have respondents switching between the status quo and the offered (hypothetical) products to calculate the relative

importance for the various attributes [13]. Additionally the finding for the utilities of the risk of exacerbations was also counterintuitive: The higher the probability of an exacerbation, the higher the utility. One explanation for this could be the characteristics of discrete choice analysis, i.e. that the (positive) impacts of the other attributes traded the negative impact of this attribute out. Additionally only few children experienced (very) often shortness of breath or much asthma attacks in the last four weeks in advance of the study. Maybe caregivers are less risk averse on this attribute when comparing it to the other three.

In this application the discrete-choice conjoint analysis requires respondents only to indicate whether they prefer one scenario over another. Moreover, it was possible to use the status quo as the reference scenario, permitting to couch this ranking in terms of a decision to purchase the product. The conjoint method has been used for decades in other research disciplines, notably consumer market research, but has only recently started to be used to study asthma. Osman et al [27] used conjoint analysis to rank asthma symptoms. Another study [29] investigated preferences for a limited number of aspects (need for blood test monitoring, frequency of dosing, and route of administration) for asthma controller medication. To our best knowledge this study is the first one, which analyzed the impact of various treatment attributes on the relative importance of caregivers for their pre-school children's asthma treatment. Obviously the sample size is relatively small due to budget restrictions, anyway the results should be important in the ranking of attribute's importance in pre-school children in chronic diseases. Furthermore the children who participated in the present study are not representative and thus the generalisability of the results is uncertain; e.g. the children were typically first-born children with very mild asthma and working mothers with university degrees. Hence the following findings have to be interpreted always in the background of the cohort characteristics. The findings of this study based on the aggregated results from 42 caregivers with children having asthma and/or wheezing condition can be summarized as follows. Caregivers focused primarily on the effectiveness of a treatment (episode free days). Ranking in terms of importance of expenses, availability of long-term effects and risk of exacerbation is strongly dependent on the risk aversion of the caregiver.

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Appendix

Appendix A.1: Example of a card presented to respondents

	AGENT A	**AGENT B**
Episode free days	180 episode free days per year	220 episode free days per year
Exacerbation	Risk of exacerbation: 10% of patients develop a mild to severe exacerbation	Risk of exacerbation: 16% of patients develop a mild to severe exacerbation
Information availability	Information available on long-term effects in children between 4 years and 14 years of age	Information available on long-term effects in children between 4 years and 14 years of age
Out-of-pocket expenses	$20	$50
	O	O

Chapter 5: Willingness-to-pay for caregivers of children with asthma or wheezing conditions

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Abstract

Background: Nearly 5 million children in the United States are affected by asthma, which is more than 5 percent of the population younger than 18 years. In children four years or younger, the prevalence increased 160 percent from 1980 to 1994. There are several effective drugs that relieve the symptoms of asthma and others are currently being developed but even when these medications are prescribed, they may be underutilized because parents fear the possibility of adverse events. There is no knowledge whether caregivers would be willing to pay (WTP) for safe and effective medications in general.

Material and Methods: In a conjoint analysis, the status quo and hypothetical treatment options are defined by four attributes: Episode-free days, risk of exacerbation, information available on the long-term impact of the treatment, and out-of-pocket expenses. Based on random utility theory, a binary purchase decision equation is specified and estimated using probit. Several tests were performed with regards to the scaling of the attribute variables, the linearity of the utility function used, and the derivation of a final model.

Results and conclusions: Marginal willingness-to-pay per month for 20 additional episode free days due to a new treatment turns out to be US$ 6.00. An interesting question from the (industry) policy point of view for possible new products is the amount of WTP for the product as a whole. Assuming that the final model is correctly specified, the (negative) constant may be interpreted as indicating that caregivers feel confident with the asthma treatment options already on the market and having hence not a positive relation to a new treatment.

Introduction

Asthma is a chronic disease that effects between 9 and 12 million persons in the United States [1] and is the most common chronic disease of childhood [2]. Nearly 5 million children in the United States are affected by asthma, which is more than 5 percent of the population younger than 18 years [3]. Asthma is the leading cause of lost school days in children [4, 5]. In children four years or younger, its prevalence increased 160 percent from 1980 to 1994. There are several effective drugs that relieve the symptoms of asthma, and more are currently being developed. However, compliance is far from perfect because parents as caregivers fear the possibility of adverse drug reactions. The objective of this study is to measure the importance of these concerns in comparison with the benefits of treatment using willingness-to-pay (WTP) estimates derived from a discrete-choice experiment (DCE).

For an economic evaluation (such as a discrete-choice analysis) of treatments in diseases such as asthma, where a substantial impact is on quality of life rather than survival, it is crucial to be able to incorporate the effects of the new therapies on quality of life and include those effects in the economic evaluation. Since there are many health insurances in the US that have a co-payment rate for the insured in their contract, considerations of relative effectiveness could be complemented by WTP estimates. Within health care there is substantial evidence to suggest that, in addition to the treatment outcome (that is, the effectiveness), other aspects of the process of receiving treatment are also important for individuals [6, 7, 8, 9]. The present study is analyzing hypothetical products for the treatment of (pre-school) asthma defined by four attributes. The target population is children with a maximum age of 4 years. Obviously the possibility to ask the children themselves was naturally limited and hence the caregivers answered for them.

The purpose of this study is to calculate, using discrete choice analysis, the willingness-to-pay of caregivers with asthmatic children for different (hypothetical)

treatments defined by four attributes. Additionally the marginal willingness-to-pay for an improvement in efficacy (episode free days) was analyzed. Furthermore the analyses were done for the whole study cohort as well as for various risk averse groups.

Materials and Methods

The DCE[1] performed in this study rests on Lancaster's theory of demand [10], with states consumer value not so much the quantities of consumer goods but their qualities and attributes. In the present context the consumer is a caregiver of at least one asthmatic child with the age of less than four years, and the commodities in question are treatment options defined by four attributes. Thus the preferences of caregivers substitute for those of their patients (which would have been far more difficult to investigate). Caregivers were asked to choose between pairs of asthma treatments for their child, viz. a fixed status quo and a new (hypothetical) alternative whose attribute levels changed in the course of the DCE. Attributes and their levels were pre-tested in face-to-face interviews with six caregivers in the autumn of 2005.

Table 1: Characteristics of individuals from the pre-test

n = 6 caregivers	Percent	Cumulative Percent
Gender		
Female	83.3	
Age		
≤ 35 years	66.6	
> 35 years	33.3	100
Number of children ≤ 4 years		
1 child	50	
2 children	50	100
Most important attributes		
Efficacy (episode free days)	83.3	
Ease of handling	50	
Side effects (exacerbation)	100	
Long-term information available	83.3	
Out-of-pocket expenses	83.3	
Number of administrations per day	66.6	
Time for administration	66.6	

Original attributes were ease of handling, efficacy (episode-free days), time for administration of treatment, number of administrations per day, side effects (risk of asthmatic exacerbation), information on long-term effects in children between 4 and

[1] The study protocol was conducted in accordance with the Declaration of Helsinki and approved by local ethics committees, and all caregivers gave written informed consent.

14 years of age (provided by the FDA) and out-of-pocket cost. The presence or absence of side effects (EXACERBATION) was deemed important without exception (see table 1). The other retained attributes are episode free days (FREEDAYS), available information provided by the FDA (INFORMATION), and the out-of-pocket cost of the treatment (EXPENSE).

Table 2: Product attributes and levels retained in the main survey

Attributes	Label	Levels	Value labels
Episode free days	FREEDAYS	Increase from 180 to 200 episode free days per year	200
		Increase from 180 to 220 episode free days per year	220
		Decrease from 180 to 160 episode free days per year	180
		Decrease from 180 to 140 episode free days per year	140
Exacerbation	EXACERBATION	Risk of EXACERBATION: 6% of patients develop a mild to severe EXACERBATION	6
		Risk of EXACERBATION: 10% of patients develop a mild to severe EXACERBATION	10
		Risk of EXACERBATION: 16% of patients develop a mild to severe EXACERBATION	16
Information about long-term effects by the FDA available	INFORMATION	INFORMATION available on long-term effects in children between 4 years and 14 years of age	1
		No INFORMATION available on long-term effects in children between 4 years and 14 years of age	2
Out-of-pocket EXPENSES	EXPENSES	$10 per month	10
		$30 per month	30
		$50 per month	50

The levels of attributes were defined as follows (see table 2). FREEDAYS, symbolizing the change in the number of episode-free days from a baseline value of 180 days per year [14]. Increases are to 200 and 220 days, decreases, to 160 and 140 days, respectively. EXACERBATION varies between 6%, 10% and 16%, indicating the share of patients who develop mild to severe exacerbation. A recent study with adults has shown that mild to moderate asthmatic exacerbation causes a marked decrease of well-being [15]. This is assumed to hold true in pre-school

children. As to INFORMATION on long-term effects specifically in children between 4 and 14 years of age, a study has found that caregivers are concerned if this information is locking. about the missing long-term effects of asthma treatment in pre-school children [17]. Finally EXPENSES ranges from $10, $30 to $50. Status quo treatment (see table 3) was defined as having 180 episode-free days per year and a 10 percent risk developing mild to severe exacerbation of asthma with information provided by FDA and monthly out-of-pocket cost of $20.

Table 3: Status quo treatment – definition by attribute levels

Attributes	Levels
Episode free days	180 episode free days per year
EXACERBATION	Risk of EXACERBATION: 10% of patients develop a mild to severe EXACERBATION
INFORMATION availability	INFORMATION available on long-term effects in children between 4 years and 14 years of age
Out-of-pocket EXPENSES	$20 per month

Since these attributes have 4, 3, 2 and 3 levels, respectively the number of scenarios amounts to a total of 72 (= 4*3*2*3). This number would cause interviews of excessive length. Using the ORTHOPLAN procedure of SPSS, the design was reduced to 16 scenarios while this still permits to infer utility values for all combinations of attribute levels [13]. All study participants had to answer these 16 variants, whose sequence was randomized to avoid possible ordering bias [17]. Each time respondents had to indicate whether or not they preferred the treatment or the status quo (for a sample card presented to study participants, see Appendix A.1).

Due to financial constraints, only 42 respondents were included in the study. However, to test the validity and significance of parameter estimates, a Monte-Carlo simulation yielding comparison estimates was also performed. The survey was conducted online in February 2006. The questionnaire also covered socioeconomic characteristics, subjective health status (chronic or other diseases) of the caregiver, specifics of the asthma treatment, and diagnosis of the physician.

Choices of caregivers are hypothesized to be governed by a common utility function, $U_k = U(Z_k)$, where U_k denotes their utility in scenario k, which depends on Z_k, the vector of attribute values pertaining to k. Any alternative, which may affect choice, is included in the vector of measured attributes z ε Z [11]. For instance, the change in the number of episode-free days from the status quo constitutes an element of the attribute vector.

Since income Y and out-of-pocket cost p_k determine the number of units x_k of the good that can be purchased, maximum attainable utility not only depends on permit attributes but income and prices. Thus the indirect utility function can be written,

$$V_k = V(z_k, p_k, Y) = U\left[Z_k^*\right] \quad (2)$$

The marginal rate of substitution between two attributes m and n is given by the ratio of marginal utilities, which indicates the relative subjective importance of them,

$$MRS = \frac{\partial V_k / \partial z_{km}}{\partial V_k / \partial z_{kn}} \quad (3).$$

If the variable n in Equation (3) is assumed to be price in the presented context, this can be interpreted as the marginal willingness-to-pay for attribute m.

A vector of socioeconomic characteristics h is introduced into the function to reflect the variability of tastes across the population to which the model of choice behavior applies [12], $V_k = V(z_k, p_k, Y, h)$ (4)

It is assumed that the chosen treatment maximizes the individual's utility, in keeping with the theory of *homus economicus* [11]. However, to the observer the determinants of utility are never fully known causing behavior to seemingly have a random component. Accordingly, the choice probability of alternative k is equal to the probability that the (indirect) utility of alternative k, V_k, is greater than or equal to the utility of alternative q,

$$\Pr(k) = \Pr(V_k > V_q), \tag{5}$$

where Pr(k) is the probability of the caregiver choosing alternative k. In general, the random utility of an alternative can be expressed as a sum of observable (or systematic) and unobservable components [13],

$$V_k = W(z_k, p_k, Y, S) + \varepsilon_k \equiv W_k + \varepsilon_k \tag{6}$$

With this result, equation (5) can now be rewritten as

$$\Pr(k) = \Pr(W_k + \varepsilon_k > W_q + \varepsilon_q) = \Pr(\varepsilon_q > W_k - W_q + \varepsilon_k) \tag{7}$$

Therefore the random element must be dominated by systematic differences in utility. For further analysis it is assumed that the error term ($\varepsilon_q - \varepsilon_k$) is standard normally distributed. With this assumption, the Probit model can be applied to estimate Pr(k). Furthermore, assuming the indirect utility function to be additively separable, the determinants of V that do not differ between scenarios q and k (in particular Y and S) drop out of the equation.

Results

Descriptive statistics

In table 4, descriptive statistics of the caregivers with regard to the dependent and explanatory variables are reported. Of all caregivers participating in this study, 19% came from the Eastern United States, 33% from the Midwest, 35% from the South and 11.9% from the West. Nearly all caregivers who took part in the survey are female (92.9%), while 7% of caregivers are fathers or grandparents. The respondents on average have one child. 40% were working full-time and 45% were homemakers. Most of the study participants reported not to smoke (71.4%), whereas 16.7% reported to smoke about one pack of cigarettes per day. The reason for the high proportion of non-smokers is to be found in the fact that the majority of caregivers have also diagnosed asthma (92.9%) or wheezing conditions (28.6%).

Caregivers were also asked how confident they are in knowing what they do when thinking about their overall ability to take care of their family's general health – eating right, getting check-ups, taking medicine, and deciding when to see the doctor. The median for this is 3.5 (standard deviation of 0.89), with 1 equivalent to "not at all confident" and 5 "Extremely confident". Overall 42.9% of respondents agreed with the feeling "very confident" (rating of 3), and another 26.7% agreed with feeling "extremely confident" (rating of 4). There, 31% felt fairly or somewhat confident, while 69% felt very or extremely confident. These descriptive findings suggest that administration of drugs to the children should be relatively good.

In 18% of cases, physicians never told the caregiver the diagnosed severity of their child with asthma. Thus, while 21.4% of caregivers rated the severity of their child as very mild, no physician gave the condition this low rating, likewise 4.8% of all cases, physicians diagnosed the children as having severe asthma, compared to 2.4% of caregivers.

Caregivers were also asked to estimate the frequency with which caregivers (in general) forget to administrate the medication to their child during a week due to

several reasons (job stress, care for other children, etc.). In various studies, this estimate is as high as 95% (with an average around 50%), [18, 19] respondents estimated that 16.7% of caregivers never forget during a week. However, when asked about their own failure, 88.1% say they forget themselves in 19% of all cases. The characteristics of the children were as follows. Anyway the first born, 33% are male and have a mean age of four years. Anyway, the second born, 64.3% were male and had a mean age of 2.8 years (standard deviation 0.96). Notice also that children with diagnosed asthma have a higher probability of having allergies in comparison to the average of the same age [19]. In this sample, 88% of children have diagnosed asthma, 26% wheezing conditions, and 71% have allergies.

Table 4: Descriptive Statistics of caregivers and their children between 0 and 4 years

	Percent	Cumulative Percent
Gender		
Female	92.9	
Age		
<30 years	28.6	
30 – 39 years	42.8	71.4
40 – 49 years	19.1	90.5
>50 years	9.5	100
Number of children ≤ 4 years		
1 child	73.8	
2 children	26.2	100
Rating of health care		
Fairly/somewhat confident	31.0	
Very/extremely confident	69.0	100
Number of children with diagnosed asthma and/or wheezing conditions		
1 child	73.8	
2 children	26.2	100
Regions		
East	19.0	19.0
Midwest	33.3	52.4
South	35.7	88.1
West	11.9	100
Relationship to children		
Mother or female guardian	85.7	
Father or male guardian	7.1	92.9
Grandparent	7.1	100
Level of education		
High school graduate (or lower)	11.9	
Some college	31.0	42.9

Associate / Bachelor's degree	40.5	83.3
Postgraduate school	14.3	97.6*
Current employment situation		
Working full-time	40.5	
Working part-time	11.9	52.4
Homemaker	45.2	97.6**
Annual household income in 2004		
< US$25,000	4.8	
US$ 25,000 – 49,999	45.2	50.0
US$ 50,000 – 74,999	19.0	69.0
> US$ 75,000	23.8	92.9***
Non-Smoker	71.4	
Severity estimation by caregiver		
Very mild	21.4	
Mild	35.7	57.1
Moderate	40.5	97.6
Severe	2.4	100
Severity diagnosis by physician		
Mild	35.7	
Moderate	40.5	76.2
Severe	4.8	81.0
Doctor never told me the severity	19.9	100
Compliance estimation for other caregivers		
< 20%	54.8	
20% - 39%	23.8	78.6
40% - 59%	7.1	85.7
> 60%	14.3	100
Own compliance estimation		
< 10%	76.2	
10% - 19%	11.9	88.1
20% - 29%	4.8	92.9
> 30%	7.1	100

Children characteristics	Percent	Cumulative Percent
Age		
≤ 2 years (child 1)	33.3	
≤ 2 years (child 2)	0	
Gender		
Female (child 1)	35.7	
Female (child 2)	66.7	
Race		
White	88.1	
Black	4.8	92.9
Other	7.1	100
Number of asthma attacks in the least 4 weeks		
Never	85.7	
A few days	9.5	95.2
Some/Most days	4.8	100
Prevalence of asthma	88.1	

Prevalence of wheezing conditions	26.2	
Prevalence of allergies	71.4	--

* Other education: 2.4%; ** Retired: 2.4%; *** Declined to answer: 7.1%

Model specification

Since 16 different asthma treatment decisions had to be evaluated by each respondent, the data are of the panel type. For this reason, a random effects probit model is used, assuming responses of a given individual to purchase questions to be correlated, while answers provided by different individuals to be uncorrelated.

The first specification test was done on the scaling of the variables reflecting product attributes. The scaling issue concerns three product attributes, the episode free days (FREEDAYS), the exacerbation probability (EXACERBATION), and the out-of-pocket expenses (EXPENSES). The discussion will focus on FREEDAYS, dealing with EXACERBATION and EXPENSES more concisely. The efficacy in terms of episode free days was scaled using two better outcomes than the status quo (180 days) and two worse outcomes: 200 and 220 for the better outcomes and 160 and 140 for the worse one. However, a linear representation of product attributes would simplify the calculation of the marginal willingness-to-pay (MWTP) values considerably. The evidence suggests that a linear representation of FREEDAYS is compatible with the data, as the effect of a reduction in episode free days from 180 to 160 days cannot be statistically distinguished from the increase in episode free days from 180 to 200 days. Also, episode free days reductions from 180 to 140 days and the improvement from 180 to 220 days have the same effect close to 22% according to the data. Therefore, the linear representation of FREEDAYS may be retained, permitting the construction of an average value of FREEDAYS and hence the calculation of MWTP at the sample means. The same tests for linearity were used for the product attributes EXACERBATION and EXPENSES. Results clearly suggest that a linear representation of all parameters is compatible with the data. A popular alternative is the quadratic utility function [20]. Therefore, the linearity of the coefficients was

analyzed by the Wald test. In view of the orthogonal design imposed, the utility function to be tested contained no interaction terms [21]. Results indicated that the quadratic terms were not significant at conventional levels, with the one exception of expenses. However, the estimated coefficient of $(EXPENSES)^2$ turned out so small as to make the linear alternative, evaluated at the mean cost, indistinguishable from the quadratic. A likelihood ratio test indicated that the exclusion of all quadratic terms does not entail a significant loss of explanatory power. Therefore, an indirect utility function linear in product attributes seems to serve as a sufficient local approximation to its true counterpart (which merely needs to be quasiconvex in price).

Up to this point, the specification tests involved only the product attributes because individual characteristics should be irrelevant in the choices analyzed if the utility function is assumed to be additively separable in product attributes and socio-economic characteristics. To test this assumption a model was estimated including interaction terms between socioeconomic variables and EXPENSES. From an economic point of view this can be justified since these interaction terms reflect the marginal utility of money, which varies with personal characteristics [22]. However, all interaction terms lacked statistical significance. In addition a likelihood ratio test indicated clearly that including interaction terms does not improve goodness of fit of the model. This finding is in agreement with the assumption of a utility function which is additively separable.

Table 5: Random effects probit estimates for the final model

Variable	Coefficient	Standard error	z	P>|z|
FREEDAYS	.0069*	.0024	2.85	0.004
EXACERBATION	-.0109	.0117	-0.93	0.351
INFORMATION	-.3447**	.1039	-3.32	0.001
EXPENSES	-.0232***	.0036	-6.51	0.000
CONSTANT	-.7936	.4990	-1.59	0.112
Number of observations	756			

Chi² (4)	52.48		
Prob > chi²	0.0000	**Rightly predicted:**	0.677

* (**, ***) Coefficient different from zero with an error probability of 5% (1%, 0.1%).

The estimates of the final random effect probit model (which contains only the four product attributes in linear form, including EXPENSES) are presented in table 5 for the original data. All product attributes are highly significant but EXACERBATION and the constant. This is of particular interest since the attribute exacerbation was one of the four most important attributes in the pre-test interviews. One possible reason why this attribute is non significant is the low number of respondents. Due to budget restrictions, only 42 respondents could be included in the survey. However, to improve the validity and significance of the study the data have also been simulated by 100 Monte-Carlo iterations. For this the binomial distribution was assumed for the simulation of the outcome "Scenario". For the caregiver's socio-economic characteristics a beta-pert distribution was assumed to stay within the calculated ranges of the parameters given by the study participants [23]. It turned out that also the attribute EXACERBATION is highly significant when using 100 iterations (see table 6), which was used as having 100 respondents.

Table 6: Random effects probit estimates for the simulated data (100 Monte-Carlo iterations)

Variable	Coefficient	Standard error	z	P>|z|
FREEDAYS	.0078***	.0016	4.92	0.000
EXACERBATION	-.0283**	.0086	-3.28	0.001
INFORMATION	-.5011***	.0702	-7.14	0.000
EXPENSES	-.0216***	.0023	-9.53	0.000
CONSTANT	-.5264	.03134	-1.68	0.093
Number of observations	1600			
Chi² (4)	142.48			
Prob > chi²	0.0000		**Rightly**	0.689

	predicted:

* (**, ***) Coefficient different from zero with an error probability of 5% (1%, 0.1%).

Willingness-to-pay

The calculation of MWTP for an improvement or reduction of episode free days is based on Equation (3). Since the indirect utility function is linear in its arguments, the marginal rate of substitution between the change in episode free days and the out-of-pocket expenses for a treatment of caregiver's child amounts to a division of the regression coefficient pertaining to FREEDAYS by the coefficient pertaining to EXPENSES.

MWTP per month for 20 additional episode free days due to a new treatment turns out to be US$6.00 (=-0.0069/-0.0231). A standard prediction in the theory of health economics is that individuals with a higher risk aversion should have a higher MWTP for a better outcome like an improvement of episode free days [24]. However as explained before, risk aversion is one of the personal characteristics that should not influence the decision.

An interesting question from the (industry) policy point of view for possible new products is the amount of WTP for the product as a whole. Assuming that the final model is correctly specified, the (negative) constant may be interpreted as indicating that caregivers feel confident with the asthma treatment options already on the market and having hence not a positive relation to a new treatment. From this benchmark, one may integrate the MWTP over the four attributes distinguished to obtain WTP for the product as a whole. As shown in table 8, a treatment having average features with regard to each of the three attributes distinguished evokes a small but positive WTP (US$1.65). The attributes for this average product is defined as having no improvement in episode free days, a probability of 6% to develop an exacerbation and information available by the FDA. The maximum WTP (US$13.54)

for a new asthma treatment could be achieved with a maximum of improvement in episode free days (220 days per year), 6% probability of exacerbation and information available by the FDA. Out of the 16 variants described, one fourth of the treatment options have a positive average WTP. The negative WTP observed raises the issue of future product development and provision of information to potential users. As can be gleaned from table 8, one increment on the scale of FREEDAYS (4 levels) is worth US$0.30 (=0.0069 / 0.0232). This means that a status quo of 180 episode free days [14] lead to WTP of US$53.53 with everything else held constant. In the case of EXACERBATION, this figure amounts to a negative amount of US$0.47 per percentage point of exacerbation probability. The available information from the FDA is worth US$14.86. Therefore, assuming equal productivity of R&D efforts, these efforts should be directed at improved efficacy (episode free days). Also, information about improvements and safety may prove of particular importance for encouraging the purchase and use of (new) asthma treatments for children.

Table 7: Willingness-to-pay (WTP) for specified asthma treatments in US$

	WTP for a specified asthma drug in US$	**Attributes (FREEDAYS, EXACERBATION, INFORMATION)**
Mean WTP	1.65	180 / 6 / 1
Maximum WTP	13.54	220 / 6 / 1
Minimum WTP	-29.80	140 / 16 / 2

Discussion and Conclusion

To the best of our knowledge this study is the first one, which analyzed the impact of various treatment attributes on the willingness-to-pay of caregivers for their pre-school children. Obviously the sample size is relatively small due to budget restrictions, however the results should be important in the rating of willingness-to-pay and utility estimations in pre-school children in chronic diseases such as asthma. Due to the fact that individuals have difficulties when dealing with probabilities [25], the measurement of the MWTP for an improvement in episode free days (using probability) may lead to particular challenges. First, the individuals concerned probably are not only interested in the aspect of the change in efficacy (assumed to be episode free days) but may consider other aspects of asthma treatment, such as the possibility to develop an asthmatic exacerbation or available information by the FDA (information on long-term effects in children between 4 and 14 years of age) as well as expenses. Secondly, the population of interest is of low age (between 0 and 4 years), which leads to the fact that these could not be included in the study due to natural limitations. Hence the caregivers of the target population were included in the survey as an approximation. This assumption could be verified due to the fact that the caregivers must decide which treatment (if any) should be offered to their child and to which price. Additionally it can be assumed that caregivers also want to maximize the utility (and quality of life) of their child.

Conjoint analysis requires respondents only to indicate whether they prefer one scenario over another. Moreover, it was possible to use the status quo as the reference scenario. Based on random utility theory, a binary purchase decision equation was specified and estimated using probit. Several tests were performed with regards to the scaling of the attribute variables, the linearity of the utility function used, and the derivation of a final model.

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Appendix

Appendix A.1: Example of a card presented to respondents

	AGENT A	**AGENT B**
Episode free days	180 episode free days per year	220 episode free days per year
Exacerbation	Risk of exacerbation: 10% of patients develop a mild to severe exacerbation	Risk of exacerbation: 16% of patients develop a mild to severe exacerbation
Information availability	Information available on long-term effects in children between 4 years and 14 years of age	Information available on long-term effects in children between 4 years and 14 years of age
Out-of-pocket expenses	$20	$50
	O	O

Chapter 6: Comparison of utility derivation methods: Discrete choice analysis versus utility rating score

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[****] This article has been submitted to the journal of Medical Decision Making

Abstract

Background: The purpose of this study was to evaluate, using conjoint analysis and utility rating scale from 0 to 10 separately, asthma patients' preferences for different aspects of asthma treatment and the possible existence of learning effects.

Methods: For conjoint analysis a status quo treatment and hypothetical treatment options were defined by four attributes. The respondents were asked, after they decided which treatment options they have chosen, how they would rate the importance of their decision.

Results: The utility scores derived for each scenario were relatively stable and lying between a value of 7.095 and 7.929. Only for one scenario the mean utility was estimated higher whereas the explanation for this outlier could be found in the characteristics of that treatment option, which was nearly a perfect treatment option and hence the utility score is higher than for the other products.

Discussion: It turns out that the influence of the product attributes on the score rating was statistically not significant. Even in the three scenarios where it could be shown that the attributes have a statistically significant influence two of the four attributes showed collinearity between each other. Findings of the correlation analyzes could be interpreted as a learning effect between the utility score and the scenario decisions made before.

Conclusions: Utility scores could be applied for studies, where just the overall utility for a given treatment is of interest, but as far as the product attributes are of particular interest for the utility estimation, conjoint analysis should be used.

Introduction

For an economic evaluation of treatments in diseases such as asthma, where a substantial impact is on quality of life rather than survival, it is crucial to be able to incorporate the effects of the new therapies on quality of life and include those effects in the economic evaluation. To evaluate the utilities of patients for various treatment options several possibilities are available such as rating scales, standard gamble, time tradeoff or conjoint analysis [1, 2, 3]. Conjoint analysis was originally developed for market research into consumer preferences, and is a method that investigates the relative importance of groups of attributes, e.g., products with certain properties or more abstract concepts such as treatment procedures [4, 5]. It has been applied to various aspects of health care; for reviews, see Ryan 1996 [6] or Szeinbach et al. 1999 [7]. Usually researchers are just using one of the above mentioned evaluation methods to derive utilities. The purpose of this study was to evaluate, using conjoint analysis and utility rating scale from 0 to 10 separately, asthma patients' preferences for different aspects of asthma treatment, including efficacy (episode free days), side effects (risk of exacerbation), availability of information by the FDA about long-term effects, and out-of-pocket expenses. Additionally the possibility of the existence of learning effects within the study participants within the answers for the different scenarios was analyzed.

The target population of this study is pre-school children with a maximum age of 4 years. Obviously the possibility to ask the children themselves was naturally limited and hence the caregivers answered for them. The relation between the utility derivation methods was analyzed and conclusions for further economic evaluations were done.

Methods

It is assumed that the preferences of caregivers of pre-school children with asthma could be taken as approximations for the utility of their child for a given treatment. For the present analysis caregivers were asked to choose between two hypothetical asthma treatments for their child. The decision was based on a status quo treatment versus a new (hypothetical) treatment with changed attribute levels. After this decision the caregivers chose a utility value for the chosen treatment option from a score range of 0 to 10, whereas 0 was assumed to be the worst outcome and 10 the best possible.

Conjoint analysis

The levels of attributes were defined as follows (see table 1):

Table 1: Product attributes and levels retained in the main survey

Attributes	Label	Levels	Value labels
Episode free days	FREEDAYS	Increase from 180 to 200 episode free days per year	200
		Increase from 180 to 220 episode free days per year	220
		Decrease from 180 to 160 episode free days per year	180
		Decrease from 180 to 140 episode free days per year	140
Exacerbation	EXACERBATION	Risk of EXACERBATION: 6% of patients develop a mild to severe EXACERBATION	6
		Risk of EXACERBATION: 10% of patients develop a mild to severe EXACERBATION	10
		Risk of EXACERBATION: 16% of patients develop a mild to severe EXACERBATION	16
Information about long-term effects by the FDA available	INFORMATION	INFORMATION available on long-term effects in children between 4 years and 14 years of age	1
		No INFORMATION available on	2

		long-term effects in children between 4 years and 14 years of age	
Out-of-pocket EXPENSES	EXPENSES	$10 per month	10
		$30 per month	30
		$50 per month	50

'Episode free days' (FREEDAYS), symbolizing the change in the risk to develop asthma attacks from an unknown individual level, takes on changes from 180 days (baseline [8]) to 200 and 220 days per year as well as a possible decrease in change to 160 and 140 days per year. 'Exacerbation' (EXACERBATION) varies between levels of 6%, 10% and 16% of patients who develop mild to severe exacerbation. For the FDA 'information' (INFORMATION) on long-term effects in children between 4 and 14 years of age two levels were used: Availability or non availability. The monthly 'out-of-pocket cost' (EXPENSES) ranges from $10, $30 to $50. Status quo treatment (see table 2) was defined as having 180 episode free days per year and a risk to develop a mild or severe exacerbation of 10%. Information by the FDA is available and the monthly out-of-pocket expenses are $20. Detailed information about the preference study itself was recently published [9, 10].

Table 2: Status quo treatment – definition by attribute levels

Attributes	Levels
Episode free days	180 episode free days per year
EXACERBATION	Risk of EXACERBATION: 10% of patients develop a mild to severe EXACERBATION
INFORMATION availability	INFORMATION available on long-term effects in children between 4 years and 14 years of age
Out-of-pocket EXPENSES	$20 per month

The conjoint analysis can be derived from Lancaster's theory of demand [11]. There the consumer values the quantity of product attributes at his disposal through the

purchase of a commodity. In our case the consumer is a caregiver of at least one asthmatic child with the age of less than 4 years.

According the theory of *homus economicus* it is assumed that the chosen product, or in this study the chosen treatment, maximizes the individual's utility [12]. However, to the observer the utilities are not known with certainty and are therefore treated as random variables. Accordingly, the choice probability of alternative k is equal to the probability that the (indirect) utility of alternative k, V_k, is greater than or equal to the utility of alternative q:

$$\Pr(k) = \Pr(V_k > V_q) \quad (1)$$

where Pr(k) is the probability of the decision maker choosing alternative k. In general, the random utility of an alternative can be expressed as a sum of observable (or systematic) and unobservable components of total utilities [13]:

$$V_k = W(z_k, p_k, Y, S) + \varepsilon_k \equiv W_k + \varepsilon_k \quad (2)$$

With this result equation (1) can now be rewritten as

$$\Pr(k) = \Pr(W_k + \varepsilon_k > W_q + \varepsilon_q)$$
$$\Pr(k) = \Pr(\varepsilon_q > W_k - W_q + \varepsilon_k) \quad (3)$$

For further analysis it is assumed that the error term ε is standard normal distributed. With this assumption the probit model can be applied to estimate Pr(k). Furthermore assuming the indirect utility function to be additively separable, the determinants of W that do not differ between scenarios q and k drop out of the equation [10].

Utility (rating) score

The typical rating score is shown as a line with well-defined endpoints, whereas the extreme outcomes (e.g. death and perfect health) are shown at the end of the line. In

this study the respondents were asked after they decided which treatment options they have chosen how they would rate the importance (in terms of utility) of their decision.

The rating score is relatively easy to apply and could be well understood by study participants. However there are various limitations in this method. First of all the utility score is not related to any decision and hence not related to any attribute evaluation. Therefore there is no theoretical basis with which the results could be interpreted as cardinal utility values. But for a quality index it is not enough to know the ordinal utility values for the single treatment options, or more general for the different health states. It is also important to know the differences between the utility values [2]. Furthermore the rating scale is sensitive for different biases [14] such as the end-of-scale bias. There the respondents are not willing to set the utility value in the next location to the extreme values. Another possible bias could be that individuals range their answers on the whole scale (spacing-out bias).

However it is assumed that the treatment options the caregivers have chosen in the various scenarios is maximizing their utility and hence the utility score could be taken as an approximation for their real utility of that chosen option. Of course no utility calculations can be done for other treatment options than the 16 offered to the individuals and also no computations could be done for the rejected treatment option(s).

Results

Descriptive statistics

The target population of this study is pre-school children with a maximum age of 4 years. Obviously the possibility to ask the children themselves was naturally limited and hence the caregivers answered for them.

Table 3: Descriptive Statistics of caregivers and their children between 0 and 4 years (more detailed in 9,10)

	Percent	Cumulative Percent
Gender		
Female	92.9	
Number of children ≤ 4 years		
1 child	73.8	
2 children	26.2	100
Rating of health care		
Fairly/somewhat confident	31.0	
Very/extremely confident	69.0	100
Children characteristics	**Percent**	**Cumulative Percent**
Age		
≤ 2 years (child 1)	33.3	
≤ 2 years (child 2)	0	
Gender		
Female (child 1)	35.7	
Female (child 2)	66.7	
Cough in last 4 weeks		
Never	14.3	
A few days	31.0	45.3
Some days	23.8	69.1
Most days	19.0	88.1
Every day	11.9	100
Wheezing conditions in last 4 weeks		
Never	26.2	
A few days	33.3	59.5
Some days	35.7	95.1
Every day	2.4	97.6****
Shortness of breath in last 4 weeks		
Never	57.1	
A few days	16.7	73.8
Some days	19.0	92.8
Most of the days	4.8	97.6****
Asthma attacks in last 4 weeks		
Never	85.7	

A few days	9.5	95.2
Some days	2.4	97.6
Most of the days	2.4	100
Number of asthma attacks in last 4 weeks		
0	16.7	
1 attack	50.0	66.7
2 attacks	16.7	83.3
6 attacks	16.7	100
Awakened in last 4 weeks due to asthma/wheezing conditions		
Never	38.1	
A few days	40.5	78.6
Some days	16.7	95.2
Most of the days	4.8	100

* Other education: 2.4%; ** Retired: 2.4%; *** Declined to answer: 7.1%
**** Don' know: 2.4%

In table 3, some descriptive statistics of the caregivers with regard to the dependent and explanatory variables are reported. The whole descriptive statistics were recently published [9, 10]. Nearly all caregivers who took part in the survey were female (92.9%). The average of respondents has one child. Caregivers were also asked how confident they are in knowing what they do when they are thinking about their overall ability to take care of their family's general health – eating right, getting check-ups, taking medicine, deciding when to see the doctor. Within the whole population 42.9% agreed with the statement feeling "Very confident" and another 26.7% agreed with the statement feeling "Extremely confident". Summarized 31% felt fairly and/or somewhat confident and 69% of caregivers felt very and/or extremely confident. During the last 4 weeks in advance of the survey 23.8% of children have had experienced cough on some days whereas 19% experienced this complication most days. 11.9% of children experienced cough every day. The condition wheezing was less often experienced every day (2.4%) but nearly 33% have experienced wheezing a few days in the last 4 weeks. Caregivers reported that 57.1% of their children never had shortness of breath but also 19% reported that their children experienced that

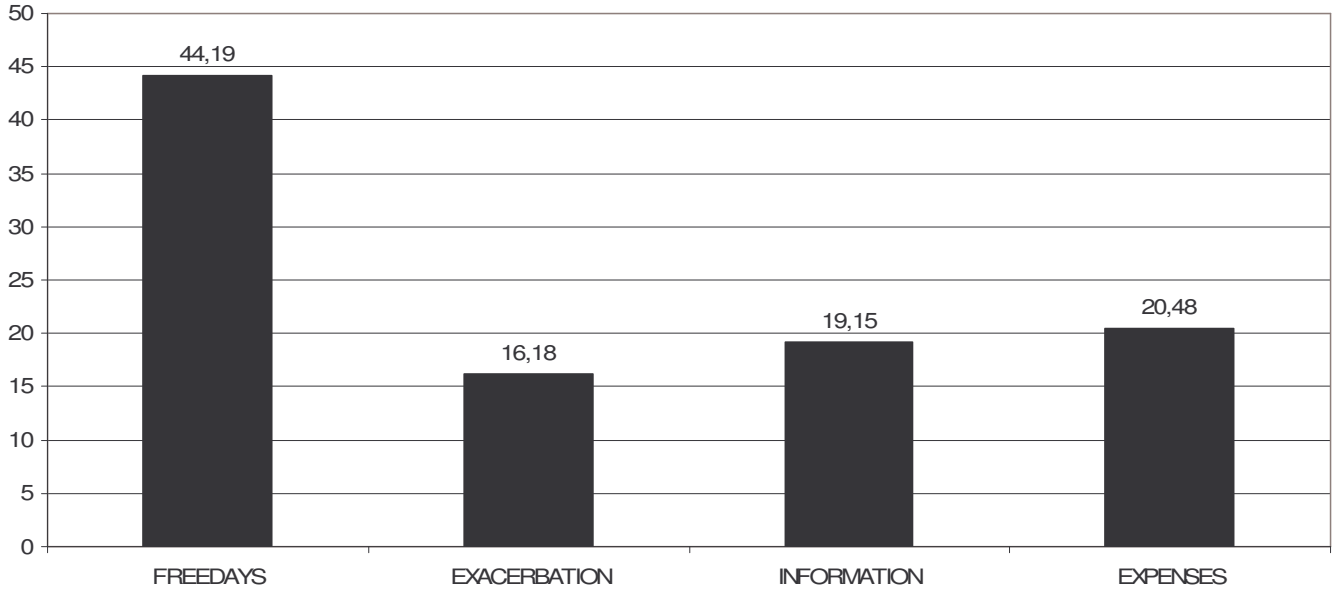
symptom some days in the last month. Asthma attacks in this study population were not that frequent (never experienced in the last 4 weeks: 85.7%) with experiences of this symptom a few days in 9.5%. Anyway of those who experienced asthma attacks 50% had one attack in the last month, 16.7% had two and another 16.7% had six asthma attacks. The possibility of awaken during the night due to asthma/wheezing conditions, such as asthma attacks, etc., was relatively frequent but not that severe: 38.1% never awakened, 40.5% awakened a few nights, 16.7% some nights but also 4.8% awakened each night.

Conjoint analysis

Results from the discrete choice decisions served as a basis for a conjoint analysis [12]. Relative importance for each product attribute as well as utility estimations for each attribute level were calculated.

For the caregivers the key attribute for an asthma drug for the treatment of childhood asthma is FREEDAYS. On a scale from 0 to 100 this attribute got the calculated relative importance of 44.2 (see figure 1). In contrast to this finding is the relative importance of the attribute EXACERBATION, which only reached 16.2, which is the most unimportant attribute of the attributes offered. Even the variable INFORMATION available on long-term effects in children between 4 years and 14 years of age was more important than the side effects (19.2). Out-of-pocket expenses per month were the second most (relative) important attribute, whereas it was only slightly more important than the attribute INFORMATION (20.5).

Figure 1: Relative importance of Factors for Treatment of Pediatric Asthma and/or Wheezing Conditions



Utility (rating) score

The utility scores for each of the 16 scenarios had nearly the same descriptive statistics in terms of mean and standard deviation (see table 4), which supports the finding of an end-of-scale bias [14].

Table 4: Descriptive Statistics of Utility estimations derived from a utility rating score

	Mean	Standard deviation
Utility 1	7.2857	2.3919
Utility 2	7.1429	2.2039
Utility 3	7.0952	1.9607
Utility 4	7.1429	2.0668
Utility 5	7.3333	1.9464
Utility 6	7.5952	1.9885
Utility 7	7.1905	2.0271
Utility 8	7.3810	1.9625
Utility 9	7.6905	2.0301
Utility 10	7.6191	1.8604
Utility 11	7.9286	1.9556
Utility 12	7.1667	1.7379

Utility 13	7.7381	1.8878
Utility 14	8.4762	1.7564
Utility 15	7.5714	1.8500
Utility 16	7.2857	2.0752

There the respondents are not willing to set the utility value next to an extreme value. The mean turns out to be in the range of 7.095 and 7.929 with one exception for scenario 14 with a mean of 8.476. The explanation for this outlier could be very easily found in the characteristics of that treatment option (see table 5): The episode free days were increased from 180 days to 200 days, the risk of exacerbation was the lowest possible level, the FDA published information about long-term effects of the drug and the monthly out-of-expenses were the lowest possible in that set. Hence these characteristics define a nearly perfect treatment option for this study. The utility score is hence higher than for the other products. The graphical display of this finding (see Appendix 1) shows that the utility score distribution for scenario 14 is rightly skewed in comparison to the other scenarios. This result can also be underlined when looking on the single scores for each scenario (see table 4).

Table 5: Definition of scenarios for discrete-choice analysis

Scenario	Episode free days	Risk of exacerbation	Information available by the FDA on long-term effects	Monthly out-of-pocket expenses
Scenario 1	180 to 200	6% of risk	No availability	$10
Scenario 2	180 to 160	16% of risk	Available	$10
Scenario 3	180 to 220	6% of risk	No availability	$30
Scenario 4	180 to 140	6% of risk	Available	$30
Scenario 5	180 to 200	10% of risk	No availability	$10
Scenario 6	180 to 200	6% of risk	Available	$50

Scenario 7	180 to 140	6% of risk	Available	$10
Scenario 8	180 to 160	6% of risk	No availability	$10
Scenario 9	180 to 160	6% of risk	No availability	$50
Scenario 10	180 to 140	10% of risk	No availability	$10
Scenario 11	180 to 140	16% of risk	No availability	$50
Scenario 12	180 to 200	16% of risk	No availability	$30
Scenario 13	180 to 160	10% of risk	Available	$30
Scenario 14	180 to 200	6% of risk	Available	$10
Scenario 15	180 to 220	10% of risk	Available	$50
Scenario 16	180 to 220	16% of risk	Available	$10

The scenarios have been stratified in the ones with an improvement in efficacy in terms of episode free days (see table 5). The utility distribution for the improved efficacy scenarios is still a normal one with scores above or equal to 7 out of 10 around 50% to 60% and scores above or equal to 8 around 30% (see Appendix A1 and table 4). However there are also possible outliers in terms of score distributions in the population in this sub analysis for scenarios 3 and 12: 47.6% of caregivers rated the scenario 3 with a score 7 or higher and 21.4% 8 or better whereas 38.1% of individuals rated the utility for scenario 12 with 7 or better and 21.4% with 8 or better. One possible explanation could be found when looking on the scenario definitions: For scenario 3 no information on long-term effects would be available for a medium price of $30, this could support the findings of the conjoint analysis that the expenses and the information availability have also a high impact on the scoring of the utility. For scenario 12 the product attributes are worsened a step more with the highest possible risk of exacerbation, no availability of information by the FDA and a medium

price. The results for the utility scores for the scenarios with a worse outcome on episode free days is not that clear. There are some scenarios which have a lower rating score on both defined thresholds but there are also other scenarios with nearly the same mean outcome. One possible explanation for this finding is that the study participants trade off desirable attributes (such as improvement of episode free days) against undesirable ones (such as high out-of-pocket expenses), and assessing which attributes are most important in determining the patient preferences for one regimen over another. This finding would support the use of conjoint analysis in such studies in comparison to simple utility rating scores.

Correlation and learning effects

From a theoretical point of view the product attributes have a significant influence on the preferences derived from the conjoint analysis [11]. This could also be shown in a recent paper [9] for this dataset. Also when thinking about a utility rating score there should be some explanatory variables which drive the study respondents to choose the utility levels they have reported. To have the highest possible comparability between preferences and utilities derived from a conjoint analysis and a rating score the same econometric model, a random-effects probit model, was applied. Beyond the attributes also socio-economic as well as interrelations between variables were included in the ranking score calculations. However, it turned out that there are no significant explanatory variables for the high and low score groups, which are driving the score estimation (see table 8). One possible explanation could be one of the general criticisms on that approach that the utility score is not related to any decision and hence not related to any attribute evaluation. Therefore there is no theoretical basis with which the results could be interpreted as cardinal utility values.

The correlations between the scenario decisions, which is assumed to be based on the treatment attributes, and the utility scores for the same scenarios could maybe anyway show a correlation between each other. Another possible correlation could

exist between scenario decisions and any of the later on done scenario evaluations. This could be explained by the fact that caregivers are showing a positive learning curve about the attribute levels and could maybe rate the scenarios later on in a different way than the others.

The possible interrelation between the scenario decision and the utility score was first analyzed. Interestingly only the decisions for scenario 2, 7 and 15 had a significant influence on the utility score estimation of the same scenario (see Appendix A2). The next step to verify that the treatment attributes are the main driver in this scenario for the utility score was to run a random-effect probit model. It turned out that the attribute FREEDAYS as well as EXPENSES are statistically highly significant (see table 7). Furthermore it can be derived from that exercise that there is collinearity between the attributes INFORMATION and EXACERBATION. This could be due to the fact that individuals interpret the information from the FDA as part of the side effects, or vice versa. Hence just for scenario 2 it could be proofed that caregivers specified their utility score according their discrete choice decision, which was based on the attributes of the treatment [9].

Table 7: Random effects probit model for the final utility estimations (Independent variable: Utilities for scenarios 2, 7 and 15 derived from score). Interrelations between the variables EXACERBATION and INFORMATION and hence these were not taken into account.

Variable	Coefficient	Standard error	z	P>|z|
FREEDAYS	-.0620***	.0159	-3.91	.000
EXPENSES	.0673*	.0220	3.07	.002
CONSTANT	9.3027***	2.4548	3.79	.000
Number of observations	126			
Chi² (2)	19.46			
Prob > chi²	0.0001		**Rightly predicted:**	.7302

* (**, ***) Coefficient different from zero with an error probability of 5% (1%, 0.1%).

The second correlation analyzes was to find a proof for the learning effect between the different scenarios i and the utility score estimations for scenario 1+i (with i=1,…16). Some findings propose that the learning curve assumption could hold (see Appendix A2), whereas the attributes of the treatment option would not have any significant effect on it. Scenario 6, for example, has a significant impact on the utility estimations for scenarios 9, 10, 11 and 14. Additionally the decision for scenario 7 and scenario 8 had both a significant impact on the utility scores 9 and 11. Furthermore scenario 12 influences utility scores 13 and 15 and scenario decision 13 has an influence on score 14. These findings could be interpreted as a learning effect between the utility score and the scenario decisions made before. The explanation why this finding was not found in more scenarios could maybe be explained by the fatigue effect, which means that the individuals were getting bored by the decisions.

The final correlation analyzes was done to find a correlation between the scenario decision i and the scenario decisions 1+i (with i=1,…16). This means it was assumed to find a learning effect between the different scenarios each individual had to decide on (see Appendix A3). The first 4 scenario decisions had each at least a statistically significant impact on the following question. Scenario 1 had additionally an influence on scenario 4 and 5, whereas scenario 2 had an additional impact on scenarios 4, 5 and 6. Scenario 3 had a statistically significant influence on questions 4,5 and also 13. Also the scenarios 6, 7, 8, 9, 10, 11 and 12 had at least a statistically significant impact on the next scenario. Interestingly the first 4 questions had each a direct impact on their next decision but not the scenarios 5 onwards. This finding could be interpreted that the learning effect at the beginning of the decision process was maybe more interesting for the individuals and hence they started to interpret the next scenario in relation to the last one but after 4 scenarios they started already to be bored and considered their learning just for some of the scenarios.

Discussion and Conclusion

This study has investigated patient preferences derived from a utility rating score and analyzed the relation between scores and preferences derived from conjoint analysis. Additionally the interrelation between the scenario decision derived from the conjoint analysis and the utility score was analyzed.

It turns out that the influence of the product attributes on the score rating was statistically not significant. Even in the three scenarios where it could be shown that the attributes have a statistically significant influence two of the four attributes showed collinearity between each others and hence only the attributes episode free days and EXPENSES had an influence. This finding indicates that there is strong evidence suggesting that the treatment attributes don't go along with a utility score. This speaks in favor of the validity of conjoint analysis as a method for measuring preferences for various treatment options defined by different attributes.

Findings of the correlation analyzes could be interpreted as a learning effect between the utility score and the scenario decisions made before. Overall the fatigue effect of the 16 scenario decisions on the utility score estimations could be more important than the learning effect. However, a learning effect between the discrete-choice scenarios i and 1+i at the beginning of the decision process could be interpreted that individuals were more interested in the study at the beginning and hence they started to interpret the next scenario in relation to the last one but after 4 scenarios they started already to be bored and considered their learning just for some of the scenarios.

The utility scores derived for each scenario were relatively stable and lying between a value of 7.095 and 7.929. Only for one scenario the mean utility was estimated higher whereas the explanation for this outlier could be very easily found in the characteristics of that treatment option: The characteristics of this scenario defines a

nearly perfect treatment option for this study and hence the utility score is higher than for the other products.

Of course the utility score could be applied for studies where just the overall utility for a given treatment or similar is of interest, but as far as the product attributes are of particular interest for the utility estimation, conjoint analysis should be used. Additional studies should be done to analyze the link between utilities derived from SF-36 or similar and preferences derived from a conjoint analysis. Especially in that case it could be interesting to see the interrelations when the product attributes would be defined similar to the SF-36 attributes and their levels.

The impact on economic evaluations, namely cost-utility analysis, depends strongly on the purpose of the study and the level of view. If the study is investigated for a micro-view dependent on various attributes the preferences derived from a conjoint analysis could be the first choice whereas the utilities derived from a utility score could be used for a macro-view where just the overall utility for various treatments and/or events are of interest.

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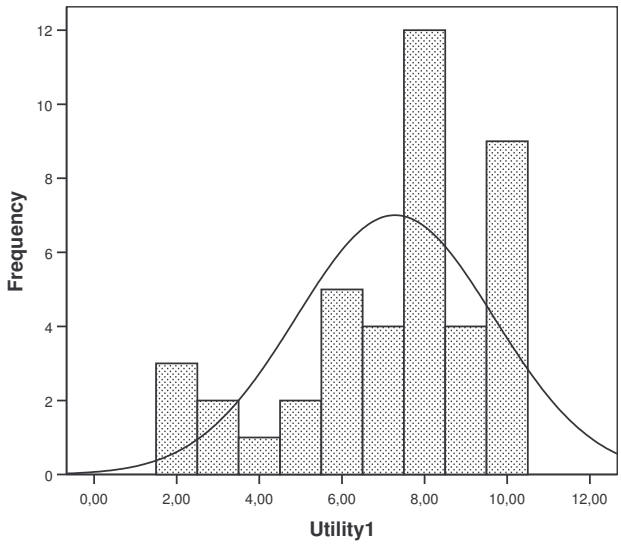
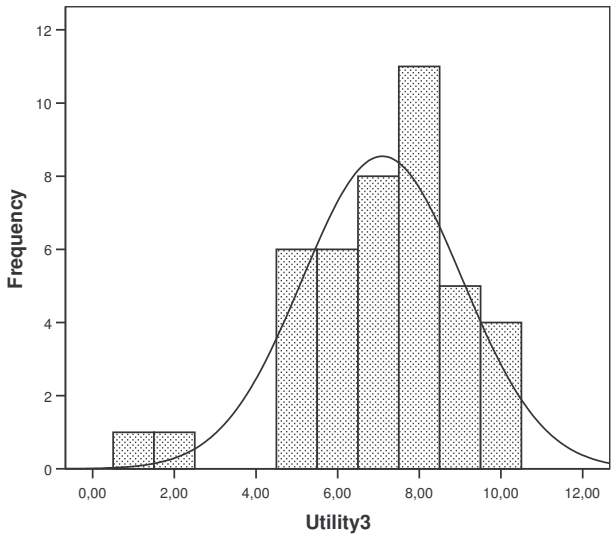
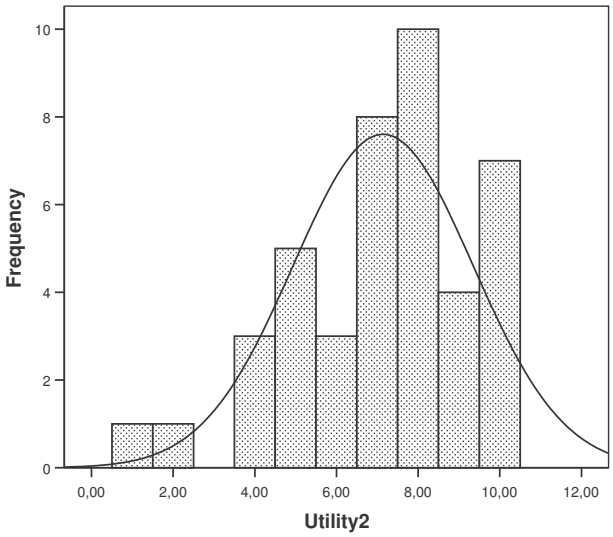
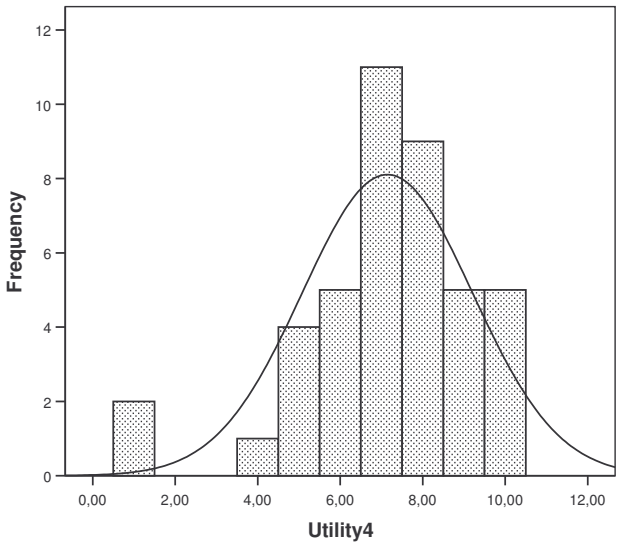
Appendix

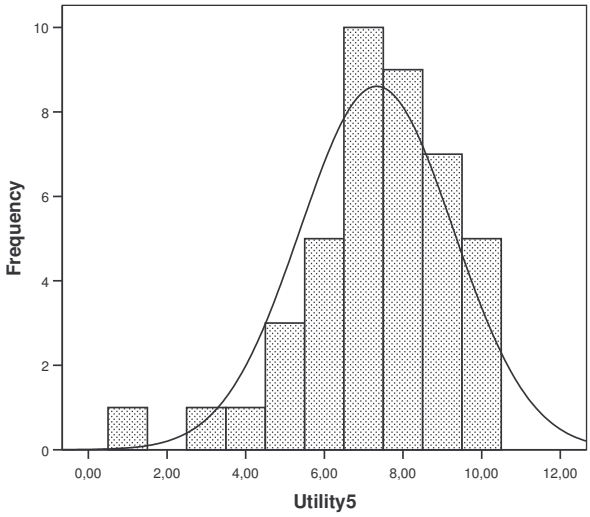
Appendix A1: Distributions, frequencies and a plotted normal distribution for the 16 utility scores







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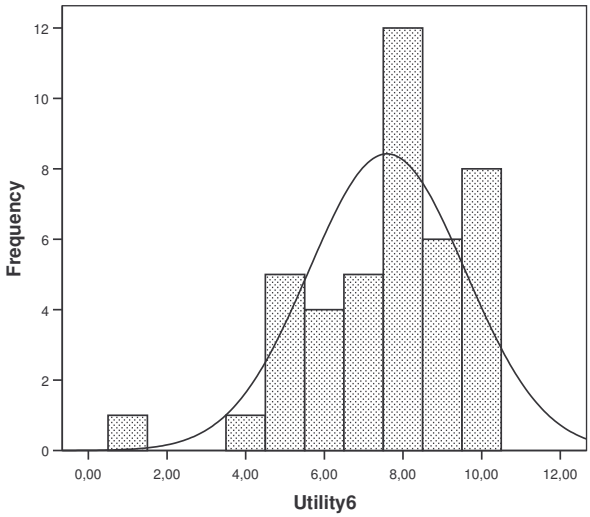
10,00
12,00
Utility5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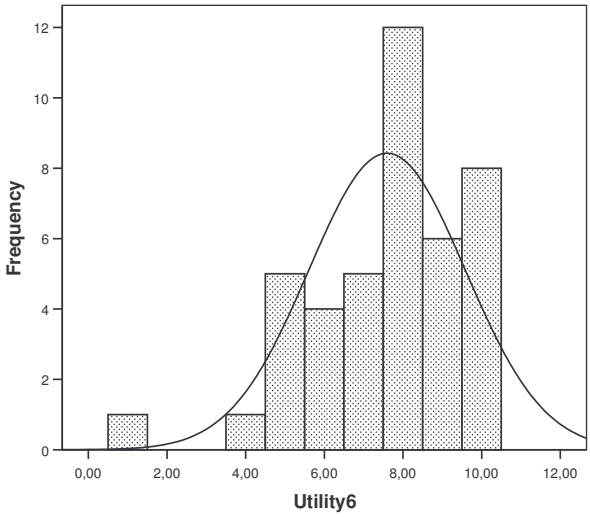
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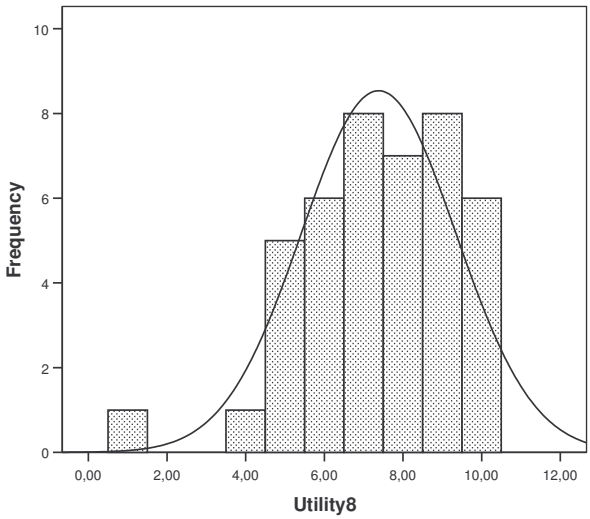
Utility6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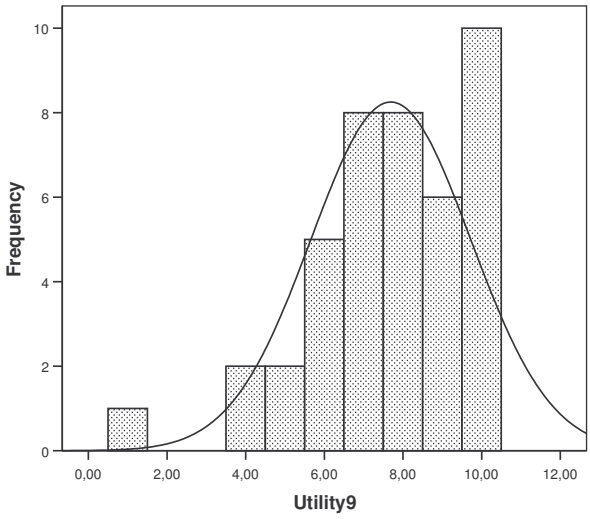
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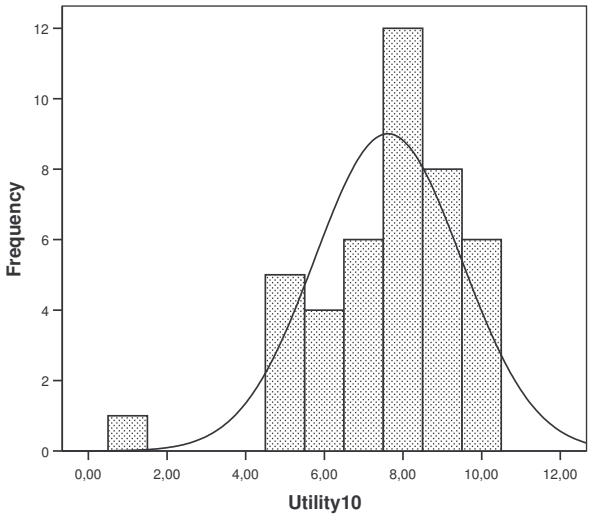
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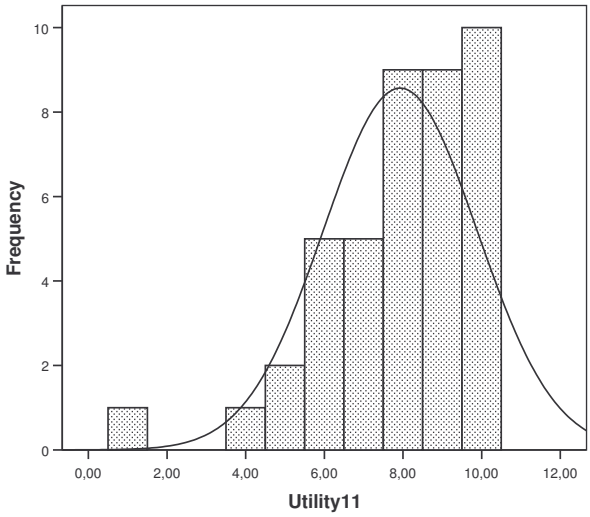
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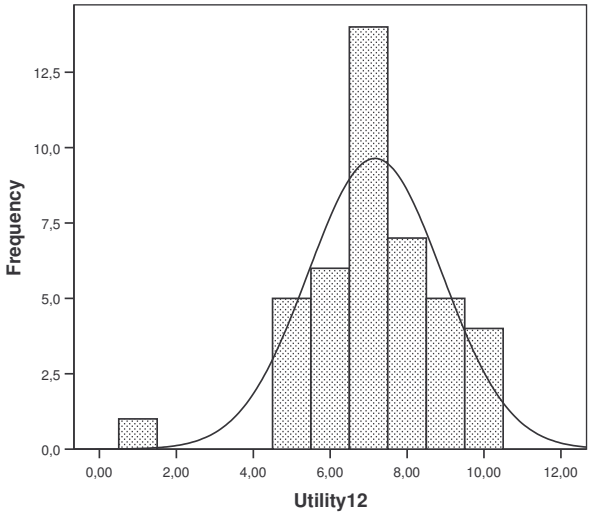
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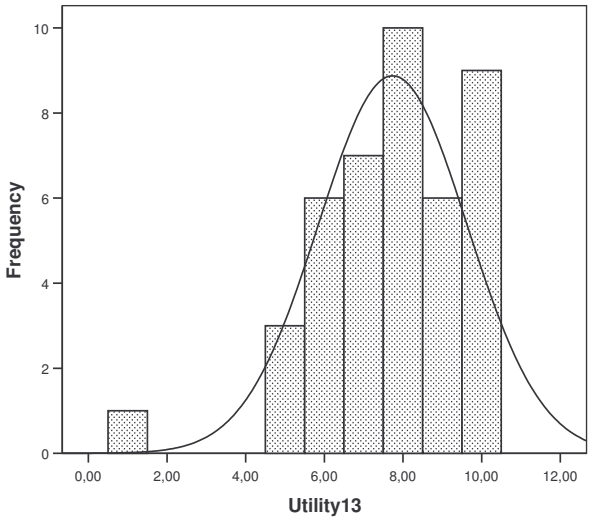
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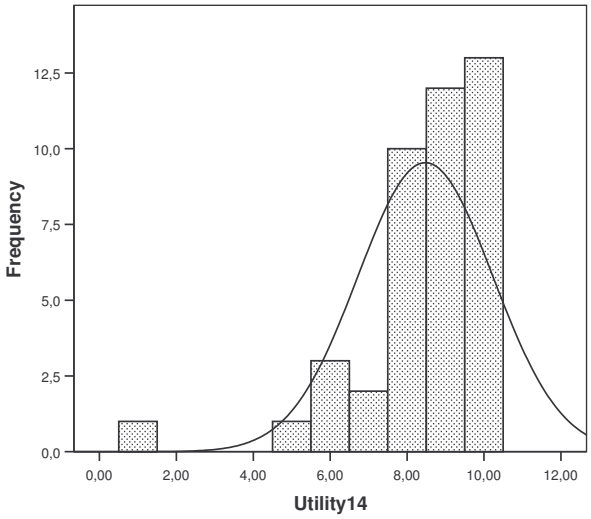
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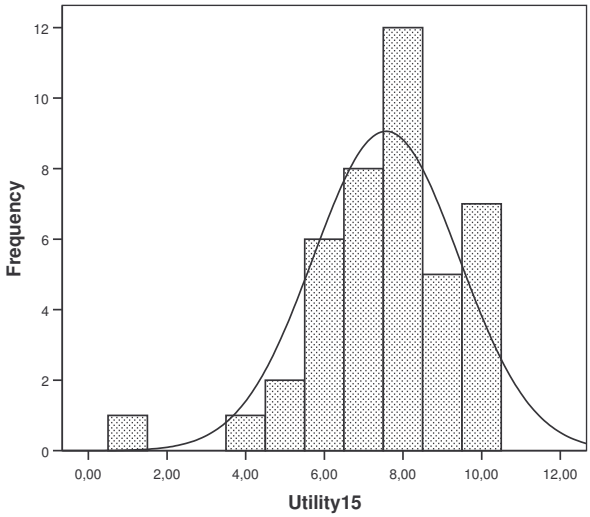
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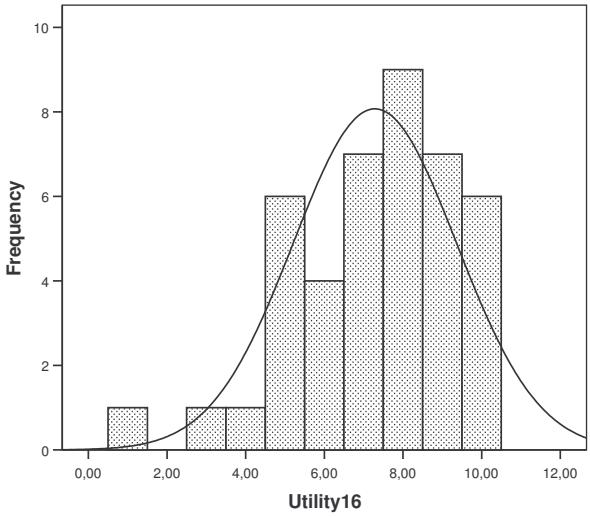
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Utility16

Appendix A2: Learning curve analyzes between discrete-choice decision and utility estimation scores - Pearson's correlation for the 16 scenarios

	Utility 1	Utility 2	Utility 3	Utility 4	Utility 5	Utility 6	Utility 7	Utility 8	Utility 9	Utility 10	Utility 11	Utility 12	Utility 13	Utility 14	Utility 15	Utility 16
Scenario 1	-.122	-.066	-.069	-.094	-.078	-.011	-.077	-.159	-.188	-.075	-.107	-.087	-.0.88	-.061	-.009	-.023
Scenario 2		**-.396****	-.284	-.242	-.064	-.074	-.219	-.072	-.090	-.204	-.024	-.078	.052	-.016	.006	-.123
Scenario 3			-.191	-.003	-.026	-.049	-.121	-.198	-.232	-.062	-.152	-.130	-.082	-.033	-.016	-.177
Scenario 4				.016	-.010	.030	.003	-.052	-.109	-.006	.021	-.184	.019	.072	.070	-.214
Scenario 5					-.030	-.129	-.195	-.162	-.238	-.113	-.131	-.186	-.082	-.043	-.005	-.243
Scenario 6						-.298	-.182	-.300	**-.346***	**-.324***	**-.367***	-.164	-.303	**-.525****	-.276	-.195
Scenario 7							.138	-.206	**-.314***	-.068	**-.331***	-.074	-.185	-.233	-.093	-.053
Scenario 8								-.158	**-.308***	-.169	**-.322***	-.155	-.237	-.302	-.209	-.194
Scenario 9									.089	.158	.154	.188	.138	.030	.166	.142
Scenario 10										.202	.167	.258	.189	.047	.208	.207
Scenario 11											.066	.174	.151	.003	.114	.241
Scenario 12												-.255	**-.308***	-.222	**-.310***	-.173
Scenario 13													-.289	**-.448****	-.284	-.038
Scenario 14														-.030	-.166	-.277
Scenario 15															**-.350***	-.280
Scenario 16																-.033

* (**) Coefficient different from zero with an (2-tailed) error probability of 5% (1%)

Appendix A3: Learning-curve analyzes between the different scenarios - Pearson's correlation for the 16 scenarios

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7	Scenario 8	Scenario 9	Scenario 10	Scenario 11	Scenario 12	Scenario 13	Scenario 14	Scenario 15	Scenario 16
Scenario 1		**.608****	.300	**.400****	**.428****	.263	.213	-.150	-.062	-.035	-.050	246.	-.108	.062	.200	.021
Scenario 2			**.340***	**.312***	**.525****	**.319***	-.091	-.246	-.102	-.057	-.082	.257	-.178	.102	.230	.257
Scenario 3				**.633****	**.701****	.033	.213	-.177	-.014	-.116	-.167	.021	**-.362***	.207	-.067	-.278
Scenario 4					**.798****	-.033	.085	-.132	.062	-.087	-.125	.053	-.271	.155	.050	-.283
Scenario 5						.166	.033	-.224	-.145	-.082	-.117	.108	-.253	.145	.078	-.125
Scenario 6							.203	.231	**.469****	**.425****	.263	.109	**.383***	-.184	**.427****	**.404****
Scenario 7								**.535****	.264	.149	-.011	-.091	.098	.106	-.085	-.283
Scenario 8									**.424****	.233	.092	-.195	**.462****	-.014	-.023	.012
Scenario 9										**.563****	**.372***	-.252	**.336***	-.282	-.124	.119
Scenario 10											**.698****	-.142	**.322***	**-.563****	-.070	.172
Scenario 11												-.203	**.461****	**-.806****	-.100	.021
Scenario 12													-.075	.252	**.364***	-.057
Scenario 13														**-.336***	.108	.290
Scenario 14															.124	.066
Scenario 15																.235
Scenario 16																

* (**) Coefficient different from zero with an (2-tailed) error probability of 5% (1%)

Chapter 7: Early retirement and the influence on health care budgets and insurance premiums in a diabetes population

STEFAN WALZER [*****]

Acknowledgement:

Preliminary results of this study were presented at the European congress of the Society for Medical Decision Making 2006 in Birmingham.

[*****] This article has been submitted to the journal of Vascular Health and Risk Management

Abstract

Objectives: To contribute to current discussions about budget impact modeling two different approaches for the impact of a new pharmaceutical product were analyzed: firstly considering the impact on annual health care expenditures only and secondly additional inclusion of lost insurance premiums due to possible early retirement in patients with chronic diseases.

Methods: The dynamic model calculates the budget impact from two different perspectives: a) the impact on health care expenditures and b) on expenditures as well as on health insurance revenues due to premiums. The latter approach could especially be useful for patients with chronic diseases who have higher probabilities of early retirement. Early retirement rates and indirect costs were derived from published data. Health Care premiums were calculated based on an average premium and a mean income. Epidemiological input data were obtained from literature. Time horizon was 10 years.

Results: Results in terms of reimbursement decisions of the budget impact analysis varied depending on the assumptions made for the insurance premiums, costs and early retirement rate. Sensitivity analyses revealed that in extreme cases the decision for accepting a new pharmaceutical product would probably be negative using approach a, but positive using approach b.

Conclusions: Depending on the disease and population of interest in a budget impact analysis not only the health care expenditures for a health insurance have to be considered but also the revenue side for an insurance due to retirement should be included.

Introduction

The use of economic evaluation in determining resource allocation is well established in a number of health services [1]. There is growing recognition that a comprehensive economic assessment of a new health care intervention at the time of launch requires both cost-effectiveness analysis (CEA) and a budget impact analysis (BIA).

BIA for new pharmaceutical products provides estimates of the likely impact of the new drug on healthcare decision-makers short and longer-term annual budgets. It is an essential part of a comprehensive economic assessment of a new pharmaceutical product and is increasingly required [1], along with CEA, before national or local formulary approval and/or reimbursement.

National regulatory agencies such as the National Institute for Clinical Excellence (NICE) in England and Wales [3], the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia [4], the Co-ordinating OFFICE for Health Technology Assessment in Canada [5], the French Transparency Committee [6] and the Pharmaceutical Benefits Board in Sweden [7] as well as managed care organizations (MCOs) in the USA, now require that companies submit estimates of both the cost-effectiveness and the likely impact of the new health care interventions on national or health plan budgets to support the reimbursement or formulary inclusion [8].

Standard methods for performing and presenting the results of CEAs are well accepted [3], the same progress has not been made for BIAs [9]. Several factors, which are not generally needed for CEA, should be part of a comprehensive BIA including the size of the treated population, incidence and prevalence estimations, market penetration rates for the new drug as well as for the main comparators. A review of the recent literature indicates that there are only a limited number of published budget impact analyses [10] and these vary greatly in the methods used.

It is recommended that a comprehensive approach to budget impact estimation be adopted, with the results being presented from both a societal perspective as well as from more limited perspectives depending on the needs of the decision maker.

Recently, Trueman and colleagues have proposed an initial framework for standardization of BIAs [8].

This paper analysis the potential impact of early retirement on health care payer's annual budgets due to a chronic and progressing disease such as diabetes mellitus. The study is first based on a theoretical analysis before a hypothetical new product in diabetes treatment is applied.

Materials and Methods

The budget of a health care payer like the social insurance payers in Germany or the private ones in the US, for instance, are mainly dependent on their expenses as well as their revenues [11]. The expenses are mainly dependent on the development of the diseases of the insureds and the related costs whereas the revenue is highly influenced by the premium an insured is paying. Once an insured is being (early) retired the real amount paid for premiums are much lower in comparison to the premiums when an insured is working full-time due to the lower income.

The following paragraph is showing the theoretical impact of early retirement as well as the impact of the drug price on the equilibrium equation for a general health insurance. The step after is to analyze a hypothetical example with a diabetes population.

Methods

The cost of illness, including the treatment costs as well as the complication costs due to a given disease, is the main driver on the health care payer budgets. The calculation of the cost of illness comprises the direct costs for complications (CoC) and the treatment costs (CoT) for the given diseases i in the years t, respectively (with i=1,.., N and t=1;…;T). The costs of illness (CoI) for n patients are calculated according to the following equation E1:

$$\text{(E1)}\quad CoI_{it} = \sum_{i=1}^{N}\sum_{t=1}^{T}\left(CoC + CoT\right)_{it} \cdot n_i$$

Additionally it is assumed that the number of complications c as well as the severity s of these are the drivers for the CoC and the market share MS_A, with an influence of price $p_{A\pm1}$, as well as

the price p_A for the drugs A (A=1,…,Z) are the drivers for the CoI. Furthermore the numbers of patients p treated in the disease population i is mainly dependent on the prevalence i_p and incidence i_i of the disease as well as the mortality rates m_i within that population. Hence equation E1 can be rewritten as

$$\text{(E2)}\quad CoI_{it}\left(c,s,d_c(MS,p)\right)=\sum_{i=1}^{N}\sum_{t=1}^{T}\left(CoC(c,s)+\sum_{A=1}^{Z}CoT_A\left(MS\left(p_{A\pm1}\right),p\right)_A\right)_{it}\cdot p_i\left(i_p,i_i,m_i\right)_t$$

The revenue side R of a health care payer balance sheet is driven by the premiums h the n insureds are paying.

$$\text{(E3)}\quad R_t=\sum_{t=1}^{T}h_t\cdot n$$

Assuming that the income Y of the insureds are influencing the real cash flow h of the revenue side and the mortality rates have an impact on the number of insureds, equation E3 can be rewritten as following

$$\text{(E4)}\quad R_t=\sum_{t=1}^{T}h(Y)_t\cdot n(m)$$

Due to the nature of some diseases early retirement is widely spread in some population parts [12]. Retirement r as a whole as a significant influence on the income Y of that population.

Assuming that no other factors have an impact on the income level equation E4 can be adapted to E5

$$\text{(E5)}\quad R_t = \sum_{t=1}^{T} h\left(Y(r)\right)_t \cdot n(m)$$

For social insurance based systems such as the German health care system, the insurance companies are mainly non-profit organizations (with the exception of the private companies). Hence the premiums for the insureds are in an equilibrium (without a need for an increase) if the revenue of the payers is equal to the costs of these. Assuming that there is only one health care payer in a given country equations E2 and E5 represent the equilibrium of the health care payer company:

$$\text{(E6)}\quad \sum_{t=1}^{T} h\left(Y(r)\right)_t \cdot n(m) = \sum_{i=1}^{N}\sum_{t=1}^{T}\left(CoC(c,s) + \sum_{A=1}^{Z} CoT\left(MS\left(p_{A\pm1}\right), p\right)_A \right)_{it} \cdot n_i\left(i_p, i_i, m_i\right)_t$$

To simplify the interpretation of E6 this is rewritten to equation E7

$$\text{(E7)}\quad \sum_{t=1}^{T} h\left(Y(r)\right)_t \cdot n(m) - \sum_{i=1}^{N}\sum_{t=1}^{T}\left(CoC(c,s) + \sum_{A=1}^{Z} CoT\left(MS\left(p_{A\pm1}\right), p\right)_A \right)_{it} \cdot n_i\left(i_p, i_i, m_i\right)_t = 0$$

First derivations with respect to retirement r and the drug price p for a new product c are as follows

(E8) $$\frac{\partial}{\partial r} = \frac{\partial Y}{\partial r} \cdot \frac{\partial h(Y(r))_t}{\partial Y} < 0$$

(E9)

$$\frac{\partial}{\partial p_i} = -\sum_{i=1}^{N} \sum_{t=1}^{T} n_i \left(i_p, i_i, m_i\right)_t \cdot \left[\frac{\partial CoT_A}{\partial MS_A} \cdot \frac{\partial MS_A}{\partial p_A} + \frac{\partial CoT_A}{\partial p_A} + \frac{\partial CoT_{A-1}}{\partial MS_{A-1}} \cdot \frac{\partial MS_{A-1}}{\partial p_A} + \frac{\partial CoT_{A+1}}{\partial MS_{A+1}} \cdot \frac{\partial MS_{A+1}}{\partial p_A} \right]$$

$$\forall A \neq 1; A \neq Z$$

Equation E8 shows the following: When the retirement rate r changes (∂ r), the income is also changed and this could be assumed to be negative. This means that retirement is assumed to have a negative impact on the income Y. When the retirement rate r is increasing the real income will be decreased. The second part of equation E8 is showing the impact of income Y on the premium function h, which could be positive: Due to the higher income it is assumed that the real amount of premiums is increasing, when assuming such a health care system as the one in Germany.

In equation E9 it is analyzed in which way a new product with price p_i has an influence on the insurance equilibrium equation E7. The number of patients n is decreasing the right-hand side of the equilibrium function E7 due to the sign of the first derivative. Additionally the costs of treatment CoT_A are of interest, whereas the sign here is mainly dependent on the price level as well as on the market share MS_A (first two parts in the bracket). Furthermore the change in costs of treatment and market share of the comparators of product A, namely A-1 and A+1, have an influence on the sign of that first derivative. Hence the sign of this equation is not clear and has to be analyzed case wise. The sign is mainly dependent on the price level of the

comparator drugs and their market share. These findings are only valid for the case $A \neq 1$ and $A \neq Z$. One special case is an innovative product without any comparators (A=1). Then the costs of treatment are changing with the price (increase) and the whole first derivative with respect to p_i is becoming negative. This would than have an influence on the revenue side which has to be increased to still fulfill the equilibrium criteria in equation E7.

Results

After the theoretical analysis of an impact of early retirement and also price changes for a product A, a hypothetical comparison follows. The market i is assumed to be the one for type 2 diabetes mellitus patients. The comparison is based on the epidemiological finding of the UKPDS, where glycaemic control was analyzed with the options of diet, sulphonylurea, metformin and insulin therapy [13].

In a usual budget impact analysis two scenarios are compared, which are usually assumed to be a world with the new possible treatment option and other available treatments and one without that new option, which is usually the environment of the current market. The market share is changed due to the fact that this new option will be available on the market.

For this hypothetical analysis it is assumed that a pharmaceutical company will develop an innovation of a so-called oral antidiabetic (OADs), which is assumed to be more effective in comparison to the OADs currently available on the market. However the insulins are still the state of the art after OADs are no more working properly in the patients in terms of HbA1c adjustment.

For the following analysis direct costs for various diabetes complications were derived from O'Brien et al. [14] whereas it was directly assumed that these US data could also be valid for the German circumstance (see table 1).

Table 1: Base assumptions for the three budget impact scenarios

Parameter	Base Case Scenario	Best Case Scenario	Worst Case Scenario
Average yearly income (€) *	35,517	35,517	35,517
Average yearly income lost due to early retirement (€)	14,207	14,207	14,207
Retirement rate for current Tx (%)	5.0	5.0	5.0

Retirement rate for current Tx and new option (%)	5.0	2.5	7.5
Premium (percentage of yearly income) *	14.0	14.0	14.0
Covered population - in both arms	83,000,000	83,000,000	83,000,000
Number of treated patients *	107,070	107,070	107,070
Prevalence (%) *	6.45	6.45	6.45
Incidence per year	1,000	500	2,000

* in the “Current Tx” and “Current Tx & NEW option” arm

Prevalence data as well as early retirement data were derived from literature [12]. The main assumptions for this analysis are summarized in table 2.

Table 2: Diabetes related complication costs derived from literature

Cost item	Costs per event (€)	Source
Hypoglycemia	384	Diabetes Care; 1995; 18(11) (16)
Retinopathy / Macular edema	71	O’Brien et al.; Diabetes Care 1998 (14)
Blindness in one eye	4,365	O’Brien et al.; Diabetes Care 1998 (14)
Cataract	2,250	Internal expert assumption
Micro- / Macroalbuminuria	78	O’Brien et al.; Diabetes Care 1998 (14)
End-stage renal disease	77,735	O’Brien et al.; Diabetes Care 1998 (14)
Neuropathy	273	O’Brien et al.; Diabetes Care 1998 (14)
Peripheral arterial disease	6,867	DRG handbook (17)
Diabetic foot syndrome	3,421	O’Brien et al.; Diabetes Care 1998 (14)
Myocardial infarction	34,597	O’Brien et al.; Diabetes Care 1998 (14)
Heart failure	12,038	DRG handbook (17)
Angina pectoris	3,102	O’Brien et al.; Diabetes Care 1998 (14)
Stroke	50,858	O’Brien et al.; Diabetes Care 1998 (14)

Assumed complication rates derived from UKPDS 33 are summarized in Appendix A1. The market for diabetes was assumed to consist just with insulin drugs and oral antidiabetics (OADs). The efficacy of the hypothetical new option on the market was assumed to be 20% better in terms of outcomes in comparison to the standard OADs. Hence the following two scenarios are analyzed: The world without the new option with the market share distribution in the following way. 38% of patients are getting a subcutaneous insulin and the rest of the treated patients are getting the OADs. All other patient groups treated with any other possibility are not taken into account.

The market share over time is changed in the way that the insulin market will have a market share of 40% after 1 year and hence the OAD market is declining by that amount. The world with the new option has the same starting point for the insulin and the OADs, whereas the new option is assumed to have no market share at all. The following three scenarios (defined on the view of a pharmaceutical company) are analyzed for the comparator world including the hypothetical new treatment (table 3):

- Base Case: The retirement rate was assumed to be 5% for both scenarios. Additionally the following market shares were assumed:
    - Market share for insulin after 4 years 45%
    - Market share for OADs after 8 years: 10%
    - Market share for the new option after 8 years: 45%
- Best Case: The retirement rate was assumed to be 2.5% for both scenarios. Additionally the following market shares were assumed:
    - Market share for insulin after 4 years 30%
    - Market share for OADs after 8 years: 0%
    - Market share for the new option after 8 years: 70%

- Worst Case: The retirement rate was assumed to be 7.5% for both scenarios. Additionally the following market shares were assumed:
    - Market share for insulin after 4 years 50%
    - Market share for OADs after 8 years: 31%
    - Market share for the new option after 8 years: 19%

Table 3: Market share for the three possible treatments over time for the three budget impact scenarios

Market Share	Current Market Share	Target Market Share (Base / Best / Worst)	Time to reach the target
Insulin: Current Tx *	38	40	1
OADs: Current Tx *	62	60	1
Insulin: Current Tx + new option	38	45 / 30 / 50	4
OADs: Current Tx + new option	62	10 / 0 / 31	8
New option	0	45 / 70 / 19	8

* Assumption: fixed market in terms of scenarios

The price for subcutaneous insulin was assumed to be €89, for the OADs €286 (see table 4). The base, best and worst case analyses were run within some stratification groups for the incidence cases and drug costs for the new option (see table 1).

Table 4: Yearly drug costs in Euro for the three pharmaceutical treatment options on the market

Cost item (€; yearly)	Base Case Scenario	Best Case Scenario	Worse Case Scenario
Insulin	286	286	286
Oral antidiabetics (OADs)	89	89	89
New option	1,000	500	1,500

The budget impact for the base case analysis, 1,000 incident cases and drug costs of €500 ranged from €58,860,034 (best case) to €99,108,673 (base case) cumulative after 10 years (Appendix A3). Assuming that the premium assumption of 14% p.a. was an equilibrium of the

costs and the expenses (see equation E7) the difference between the yearly premiums of the world with and without the hypothetical new drug ranged between 0.0034 and 0.0122, which was a proportional difference between 2.3% and 8.9% after 10 years. It turned out that the direction of the difference of the yearly premiums and the budget impact result would influence the decision makers in the same way. The new treatment option is not only more effective and has a positive impact on the health care payer's budget (in terms of cost reduction) but has also a reduction in the yearly premiums as a result due to the improvement of the early retirement rate. This conclusion can also be drawn for the third sensitivity analyses (drug price: €1,500). The only scenario where the hypothetical new drug is dominant in terms of budget impact and premium change is the analysis with an assumed drug price of €500.

The second analysis was done by taking the same assumptions as before but changing the incidence rate from 1,000 new cases per year to 500 new cases per year. For the base case analysis (drug costs €500) it can be seen that the budget impact is negative which means that the current treatment possibilities (insulin and OADs) are cheaper than the current treatment inclusive the hypothetical new treatment (see Appendix A2). But when reviewing the yearly premiums based on the early retirement rate and the costs per year, the decision maker should go with the new treatment due to lower yearly premiums, between 0.0046 (proportional: 2.6%) and 0.0167 (proportional: 10.0%). The same conclusion can be drawn when doing the analysis for a yearly drug price per patient of €1,500. Interestingly the influence on the decision maker is changed when including a drug price for the hypothetical new option to €500. With that price the budget impact is improved in terms of cost reduction with the new treatment as well as a lower premium per year.

The third analysis was run for the three scenarios described above and an incidence rate of 2,000 new cases per year (see Appendix A4). Also for this stratification analysis it turns out that the impact of the early retirement rate is much higher for the yearly premium calculations than for the budget impact. The budget impact would speak in favor of the new hypothetical

treatment for a price of €500 but not for the other two price options whereas the premiums calculations would always lead to the conclusion that the new treatment should be reimbursed by the health care payer.

Discussion

The dependency of health care payers on their revenue based on the premiums paid by their insured population and the costs mainly influenced by the cost of complications and the costs of treatment (pharmaceutical costs) was analyzed within a budget impact modeling framework. Across the ISPOR members of the Budget Impact Analysis Task Force there is no consensus at this time point whether the revenue side of the health care payers should also be taken into account within a budget impact analysis [15]. This study shows the theoretical implications of a new product if a change in the early retirement rate could be expected for a new product due to a higher efficacy in comparison to the standard treatment. The product price as well as the assumptions for the early retirement rate can change the equilibrium of a revenue-cost premium calculation for a health care payer as was derived in a theoretical model. Additionally a hypothetical comparison in diabetes patients was undergone. The theoretical results could be proofed by this study. Some assumptions had to be done, for instance on the levels of the drug prices, incidence and prevalence rates as well as the event rates for some complications which were derived from a well-known study [13]. In general it turned out that the premium differences were always in favor of the new option opportunity, which could be the fact due to the assumption of a 20% better influence on the complications. The negative influence of the new option in terms of budget impact was highly dependent on the assumed drug price and the early retirement rate.

The weakness of this theoretical study can be seen in the following points. The premium calculations are usually based on all diseases and hence on all patients as well as on the disease free population of the given health care payer. Within this hypothetical example it was assumed that only one disease area (diabetes) was of interest when analyzing the impact on the annual premiums. It was assumed that the impact of all other diseases as well as the impact of the healthy population is hold constant when comparing the two worlds of interest: Current treatment versus current treatment and new option. Additionally the impact of these groups was

assumed to be constant over time and hence no new drugs would enter the market for other diseases where a health care payer could benefit from. Also, the early retirement rates were held constant over time, which means the impact of the new drug option and also the higher early retirement risk with a higher age, was not taken into account. Within such a circumstance it can be seen that a new drug with a higher efficacy could lead to a benefit for the health care payer with two possibilities: On the one hand the new treatment possibility could reduce the costs and could hence result in an improvement for the budget impact for some scenarios and on the other hand, which could go along with the budget impact argument, the new drug could lower the complication rates which would reduce the complication costs and the early retirement rate. The last point could lead to a possible decrease in the annual premiums due to a higher revenue. This last option is not just valid assuming a non-profit health care payer like the social insurance companies in Germany, for instance, but also for private insurances looking for profits. For the latter ones the profitability would increase by the difference of the annual premiums.

The here suggested framework should be taken into account if there is any possibility of early retirement reduction due to a more effective treatment possibility. It is recommended that sensitivity analysis are not only done with the costs but also with the market share over time as well as with the incidence rates, based on epidemiological data. Further empirical research on the influence of premiums and costs on the decision making process is given a favorable opinion.

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Appendix

Appendix A1: Cumulative diabetes complication rates derived from UKPDS 33 [13] for the world with and without the new option ("Current treatment" vs "Current treatment & NEW option"). The complication rates are reported for the hypothetical diabetes cohort of 107,070 at year 0 (see assumptions).

Complication	"Current treatment"									
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Hypoglycemia	2,478	5,274	7,257	8,861	10,060	11,087	11,782	12,331	12,772	10,649
Ophthalmic disorders (retinopathy, macular edema, blindness, cataract)	12,376	23,052	31,963	39,641	46,598	52,785	58,389	63,589	68,376	72,850
Kidney system (Micro-, macroalbuminuria, end-stage renal disease)	4,835	9,460	14,175	18,373	22,431	26,438	30,321	33,827	37,141	39,842
Nerve system (neuropathy, peripheral arterial disease, diabetic foot syndrome)	4,613	9,042	13,571	18,124	22,578	26,874	30,963	35,442	40,158	44,560
Cardiovascular system	3,094	5,8839	8,651	11,365	14,038	16,619	19,142	21,398	23,713	26,014
Mortality	5,845	11,442	16,574	21,279	25,920	30,118	34,032	37,834	41,378	44,782
Complication	**"Current treatment & NEW option"**									
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Hypoglycemia	2,831	5,092	6,999	8,688	9,876	10,945	11,672	12,279	12,915	13,387
Ophthalmic disorders (retinopathy,	11,513	21,403	29,638	36,704	43,064	48,508	53,467	58,008	62,184	66,029

macular edema, blindness, cataract)										
Kidney system (Micro-, macroalbuminuria, end-stage renal disease)	4,460	8,687	12,996	16,872	20,596	24,244	27,787	30,993	34,047	36,536
Nerve system (neuropathy, peripheral arterial disease, diabetic foot syndrome)	4,286	8,348	12,423	16,517	20,489	24,283	27,819	31,706	35,773	39,509
Cardiovascular system	2,931	5,564	8,180	10,722	13,251	15,717	18,076	20,173	22,303	24,419
Mortality	5,484	10,732	15,519	19,979	24,438	28,395	32,121	35,824	39,304	42,625

Appendix A2: Budget Impact and premium differences for the three scenarios (base, best worse case) and for the corresponding (new option) cost groups for the incidence group 1,000 patients per year. Budget Impact as well as premium differences are "Current Tx" vs "Current Tx & NEW".

Incidence per year: 1,000	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
New option costs: €500										
Budget Impact: Base Case	8,8847,518	14,172,088	24,553,377	36,123,442	44,348,912	49,426,880	60,670,863	70,756,833	85,102,459	99,108,673
Budget Impact: Best Case	4,968,733	5,573,514	12,102,680	20,062,508	24,303,277	25,193,357	32,636,192	38,612,245	49,164,357	58,860,034
Budget Impact: Worse Case	7,117,511	12,480,246	20,742,754	29,663,493	36,593,758	41,611,688	50,223,934	58,257,157	68,769,327	79,312,377
Premium difference (%): Base Case	0.0013 (0.1)	0.0028 (1.8)	0.0045 (2.9)	0.0059 (3.7)	0.0071 (4.4)	0.0082 (5.1)	0.0089 (5.7)	0.0091 (5.9)	0.0088 (6.0)	0.0085 (6.1)
Premium difference (%): Best Case	0.0024 (1.6)	0.0045 (3.0)	0.0068 (4.4)	0.0087 (5.5)	0.0103 (6.5)	0.0118 (7.5)	0.0127 (8.2)	0.0129 (8.6)	0.0126 (8.8)	0.0122 (8.9)
Premium difference (%): Worse Case	0.0001 (0.1)	0.0008 (0.5)	0.0016 (1.0)	0.0022 (1.3)	0.0027 (1.6)	0.0032 (2.2)	0.0036 (2.3)	0.0036 (2.3)	0.0035 (2.3)	0.0034 (2.3)
New option costs: €1,000										
Budget Impact: Base Case	-11,008,614	-26,070,717	-36,652,501	-46,415,326	-59,806,876	-76,750,125	-88,377,410	-101,887,136	-112,177,201	-123,979,141
Budget Impact: Best Case	-28,738,462	-62,164,812	-89,744,421	-115,808,158	-145,612,915	-179,171,899	-207,231,445	-237,830,339	-265,435,969	-295,744,857
Budget Impact: Worse Case	-513,781	-2,483,397	-1,653,996	-279,004	-1,012,490	-3,858,233	-3,693,205	-4,510,308	-3,303,420	-2,494,335
Premium difference (%): Base Case	0.0013 (0.8)	0.0028 (1.8)	0.0045 (2.8)	0.0059 (3.6)	0.007 (4.3)	0.0081 (5.0)	0.0088 (5.6)	0.0089 (5.8)	0.0087 (5.9)	0.0084 (6.0)
Premium difference (%): Best Case	0.0023 (1.6)	0.0045 (2.9)	0.0068 (4.3)	0.0086 (5.4)	0.0102 (6.4)	0.0116 (7.4)	0.0125 (8.1)	0.0127 (8.5)	0.0125 (8.7)	0.0121 (8.8)
Premium difference (%): Worse Case	0.0001 (0.0)	0.0008 (0.5)	0.0015 (0.9)	0.0021 (1.3)	0.0026 (1.6)	0.0031 (1.9)	0.0034 (2.1)	0.0035 (2.2)	0.0034 (2.2)	0.0032 (2.2)

New option costs: €1,500										
Budget Impact: Base Case	-30,339,519	-65,342,035	-96,289,765	-126,743,112	-161,193,055	-199,692,095	-233,500,675	-269,927,604	-304,028,352	-340,790,018
Budget Impact: Best Case	-61,920,432	-128,931,651	-190,022,909	-249,467,842	-312,759,498	-380,302,119	-443,174,072	-509,669,424	-574,607,786	-644,072,811
Budget Impact: Worse Case	-7,619,847	-16,475,553	-22,482,132	-28,010,518	-35,849,128	-46,093,119	-53,685,334	-62,674,272	-69,947,658	-78,024,111
Premium difference (%): Base Case	0.0013 (0.9)	0.0028 (1.8)	0.0045 (2.8)	0.0059 (3.6)	0.007 (4.3)	0.0081 (5.0)	0.0088 (5.6)	0.0089 (5.8)	0.0087 (5.9)	0.0084 (6.0)
Premium difference (%): Best Case	0.0023 (1.6)	0.0045 (2.9)	0.0068 (4.3)	0.0086 (5.4)	0.0102 (6.4)	0.0116 (7.4)	0.0125 (8.1)	0.0127 (8.5)	0.013 (8.7)	0.0121 (8.8)
Premium difference (%): Worse Case	0.0001 (0.0)	0.0008 (0.9)	0.0015 (0.9)	0.0021 (1.3)	0.0026 (1.6)	0.0032 (1.9)	0.0034 (2.1)	0.0035 (2.2)	0.0034 (2.2)	0.0032 (2.2)

Appendix A3: Budget Impact and premium differences for the three scenarios (base, best worse case) and for the corresponding (new option) cost groups for the incidence group 500 patients per year. Budget Impact as well as premium differences are "Current Tx" vs "Current Tx & NEW".

Incidence per year: 500	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
New option costs: €500										
Budget Impact: Base Case	8,322,292	13,200,602	22,984,763	33,912,459	41,579,302	46,191,844	56,745,854	66,153,332	79,673,949	92,831,737
Budget Impact: Best Case	4,602,027	4,602,027	10,534,066	17,851,526	21,533,668	21,958,321	28,711,182	34,008,745	43,735,848	52,583,097
Budget Impact: Worse Case	6,592,285	11,508,759	19,174,141	27,452,510	33,824,149	38,376,653	46,298,925	53,653,656	63,340,817	73,035,440
Premium difference (%): Base Case	0.0013 (0.9)	0.0028 (1.8)	0.0045 (2.8)	0.0059 (3.6)	0.007 (4.3)	0.0081 (5.0)	0.0088 (5.6)	0.0089 (5.8)	0.0087 (5.9)	0.0084 (6.0)
Premium difference (%): Best Case	0.0023 (1.6)	0.0045 (2.9)	0.0068 (4.3)	0.0086 (5.4)	0.0102 (6.4)	0.0116 (7.4)	0.0127 (8.1)	0.0127 (8.5)	0.0125 (8.7)	0.0121 (8.8)
Premium difference (%): Worse Case	0.0001 (0.0)	0.0008 (0.5)	0.0015 (0.9)	0.0021 (1.3)	0.0026 (1.6)	0.0031 (1.9)	0.0034 (2.1)	0.0035 (2.2)	0.0034 (2.2)	0.0032 (2.2)
New option costs: €1,000										
Budget Impact: Base Case	-11,008,614	-26,002,120	-36,453,342	-46,000,992	-58,886,072	-74,875,789	-85,752,481	-98,107,186	-107,540,589	-118,061,822
Budget Impact: Best Case	-28,738,462	-62,009,423	-89,219,944	-114,620,480	-143,187,163	-174,725,971	-200,609,303	-228,166,314	-252,589,238	-278,662,119
Budget Impact: Worse Case	-513,781	-2,475,995	-1,671,224	-372,342	-1,138,886	-3,899,416	-3,928,150	-4,886,497	-4,197,019	-3,927,155
Premium difference (%): Base Case	0.0013 (0.9)	0.0028 (1.8)	0.0046 (2.8)	0.0061 (3.7)	0.0076 (4.4)	0.0092 (5.3)	0.0104 (6.0)	0.0111 (6.4)	0.0115 (6.6)	0.0117 (6.8)
Premium difference (%): Best Case	0.0023 (1.6)	0.0045 (2.9)	0.0069 (4.3)	0.009 (5.5)	0.011 (6.6)	0.013 (7.7)	0.0148 (8.7)	0.0158 (9.3)	0.0164 (9.7)	0.0167 (10.0)
Premium difference (%): Worse Case	0.0001 (0.0)	0.0008 (0.5)	0.0016 (0.9)	0.0022 (1.3)	0.0028 (1.6)	0.0036 (2.0)	0.0041 (2.3)	0.0044 (2.4)	0.0046 (2.5)	0.0046 (2.6)

New option costs: €1,500										
Budget Impact: Base Case	-30,339,519	-65,176,386	-95,691,990	-125,316,374	-158,228,845	-194,222,406	-225,112,588	-257,516,882	-287,111,454	-318,067,899
Budget Impact: Best Case	-61,920,432	-128,613,390	-188,842,320	-246,641,851	-307,072,176	-370,175,648	-427,511,437	-486,532,420	-542,643,841	-600,872,385
Budget Impact: Worse Case	-7,619,847	-16,434,486	-22,363,688	-27,761,139	-35,280,174	-44,879,832	-51,912,247	-60,000,445	-66,465,838	-73,438,798
Premium difference (%): Base Case	0.0013 (0.9)	0.0028 (1.8)	0.0046 (2.8)	0.0061 (3.7)	0.0076 (4.4)	0.0092 (5.3)	0.0104 (6.0)	0.0111 (6.4)	0.0115 (6.6)	0.0117 (6.8)
Premium difference (%): Best Case	0.0023 (1.6)	0.0045 (2.9)	0.0069 (4.3)	0.009 (5.5)	0.1104 (6.6)	0.0131 (7.7)	0.0148 (8.7)	0.0158 (9.3)	0.0164 (9.7)	0.0167 (10.0)
Premium difference (%): Worse Case	0.0001 (0.0)	0.0008 (0.5)	0.0016 (0.9)	0.0022 (1.3)	0.0028 (1.6)	0.0036 (2.0)	0.0041 (2.3)	0.0044 (2.4)	0.0046 (2.5)	0.0046 (2.6)

Appendix A4: Budget Impact and premium differences for the three scenarios (base, best worse case) and for the corresponding (new option) cost groups for the incidence group 2,000 patients per year. Budget Impact as well as premium differences are "Current Tx" vs "Current Tx & NEW".

Incidence per year: 2,000	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
New option costs: €500										
Budget Impact: Base Case	8,322,292	13,257,513	23,383,676	35,108,597	43,824,505	49,633,878	63,022,311	75,854,974	94,961,295	114,606,698
Budget Impact: Best Case	4,443,507	4,616,994	10,797,333	18,752,795	23,205,302	24,427,551	33,547,884	41,626,652	56,276,813	70,652,998
Budget Impact: Worse Case	6,592,285	11,561,286	19,479,943	28,324,620	35,467,645	40,931,960	50,784,880	60,506,065	73,878,853	87,937,344
Premium difference (%): Base Case	0.0013 (0.9)	0.0028 (1.8)	0.0043 (2.8)	0.0053 (3.5)	0.006 (4.1)	0.0065 (4.6)	0.0066 (5.0)	0.0062 (5.1)	0.0057 (5.0)	0.0051 (5.0)
Premium difference (%): Best Case	0.0023 (1.6)	0.0044 (2.9)	0.0065 (4.2)	0.0079 (5.3)	0.0088 (6.1)	0.0094 (6.9)	0.0095 (7.3)	0.009 (7.5)	0.0082 (7.4)	0.0074 (7.4)
Premium difference (%): Worse Case	0.0001 (0.0)	0.0007 (0.5)	0.0014 (0.9)	0.0019 (1.2)	0.0022 (1.4)	0.0025 (1.7)	0.0025 (1.9)	0.0024 (1.9)	0.0021 (1.8)	0.0019 (1.8)
New option costs: €1,000										
Budget Impact: Base Case	-11,008,614	-26,002,120	-36,453,342	-46,000,992	-58,886,072	-74,875,789	-85,752,481	-98,107,186	-107,540,589	-118,061,822
Budget Impact: Best Case	-28,738,462	-62,009,423	-89,219,944	-114,620,480	-143,187,163	-174,725,971	-200,609,303	-228,166,314	-252,589,238	-278,662,119
Budget Impact: Worse Case	-513,781	-2,475,995	-1,671,224	-372,342	-1,138,886	-3,899,416	-3,928,150	-4,886,497	-4,197,019	-3,927,155
Premium difference (%): Base Case	0.0013 (0.9)	0.0028 (1.8)	0.0046 (2.8)	0.0061 (3.7)	0.0076 (4.4)	0.0092 (5.3)	0.0104 (6.0)	0.0111 (6.4)	0.0115 (6.6)	0.0117 (6.8)
Premium difference (%): Best Case	0.0023 (1.6)	0.0045 (2.9)	0.0069 (4.3)	0.009 (5.5)	0.011 (6.6)	0.0131 (7.7)	0.0148 (8.7)	0.0158 (9.3)	0.0164 (9.7)	0.0167 (10.0)
Premium difference (%): Worse Case	0.0001 (0.0)	0.0016 (0.9)	0.0022 (1.3)	0.0028 81.6)	0.0036 (2.0)	0.0041 (2.3)	0.0044 (2.3)	0.0044 (2.4)	0.0046 (2.5)	0.0046 (2.6)

New option costs: €1,500										
Budget Impact: Base Case	-30,339,519	-65,176,386	-95,691,990	-125,316,374	-158,228,845	-194,222,406	-225,112,588	-257,516,882	-287,111,454	-318,067,899
Budget Impact: Best Case	-61,920,432	-128,613,390	-188,842,320	-246,641,852	-307,072,176	-370,175,648	-427,511,437	-486,511,437	-542,643,841	-600,872,385
Budget Impact: Worse Case	-7,920,432	-16,434,486	-22,363,688	-27,761,139	-35,280,174	-44,897,832	-51,912,247	-60,000,445	-66,465,838	-73,438,798
Premium difference (%): Base Case	0.0013 (0.9)	0.0028 (1.8)	0.0046 (2.8)	0.0061 (3.7)	0.0076 (4.4)	0.0092 (5.3)	0.0104 (6.0)	0.0111 (6.4)	0.0115 (6.6)	0.0117 (6.8)
Premium difference (%): Best Case	0.0023 (1.6)	0.0045 (2.9)	0.0069 (4.3)	0.009 (5.5)	0.011 (6.6)	0.0131 (7.7)	0.0148 (8.7)	0.0158 (9.3)	0.0164 (9.7)	0.0167 (10.0)
Premium difference (%): Worse Case	0.0001 (0.0)	0.0008 (0.5)	0.0016 (0.9)	0.0022 (1.3)	0.0028 (1.6)	0.0036 (2.0)	0.0041 (2.3)	0.0044 (2.4)	0.0046 (2.5)	0.0046 (2.6)

Chapter 8: Conclusion

The conclusion is confined to a brief discussion of possible impacts of the results on medical decision-making. The first essay on a new approach of cost-effectiveness analysis provides an interesting and empirically testable model framework. It has to be discussed whether it is worthwhile to assume the time trend of the discount rate to use this approach or whether it is easier and more pragmatic to stick with the current framework. In a hypothetical example the model showed differences between the current approach and the approach suggested in the essay whereas this has first to be proven by a face-to-face comparison of a real world cost-effectiveness project.

Essays two and three show the preferences of caregivers for an asthma treatment for their children aged 4 years and younger. The general criticisms about discrete choice experiments are also valid here: The results should only be interpreted with the attributes used for the study. Additionally the relatively small sample size should be considered as a crucial element, whereas the robustness of the analyses was tested by a Monte-Carlo simulation. These findings show once again that the conjoint analysis is a useful tool for economic evaluation studies and could be improving the decision-making process by understanding the preferences of the consumers or their caregivers. Essay four shows that there could be some learning effects, especially for some of the scenarios but overall it could not be proven that there is a significant effect of it on the results. This finding should be taken into consideration when designing and implementing or evaluating conjoint analyses.

The final paper gives a new framework for budget impact modeling: Decision makers, such as health maintenance organizations, hospitals or insurances are more and more interested in the budget impact of a new product. The approach suggested in the essay is the first one where not only the cost side but also the revenue side of such a decision-maker is taken into consideration. The early retirement rate has an impact on the real premium an individual is paying and hence a new product, which is decreasing early retirement, could even be worthwhile when it is more costly in

comparison to other products. That approach shows that not only the cost side but also the revenue side should be taken into account in such (Budget Impact) models.

Curriculum vitae

QUALIFICATIONS HIGHLIGHTS

- PhD Thesis: 5 essays in Health Economics
- 3 years pharmaceutical industry experience
- 3 years economic evaluation experience
- 3 years pricing and market access experience
- Expert in economic evaluation models and simulations as well as quantitative pricing studies

PROFESSIONAL EXPERIENCE

Senior Analyst, Health Economist, MA (Econ)
Analytica International GmbH. Loerrach, Germany and New York, USA **2004-09/2006**
Consultant firm with expertise in HEOR, pricing and market access and clinical trials (www.analyticaintl.com)

Expertise / Projects:

- Designed Health Economic models (CE, CU, CM, NHB, BIM) to support pharma market access
- Developed economic evaluation models including Markov models and Monte-Carlo simulations to support pharmaceutical company's marketing and price and reimbursement applications
- Provide the input and the information of Global Value Dossiers for country affiliates
- Delivered solid evidence based value arguments and data by supporting pharmaceutical companies in quantitative studies, utility and demand estimations
- Implemented marketing studies to predict demand for a new product under alternative attributes and price strategies (discrete choice demand) and analyze pricing structures
- Therapeutic Areas: Oncology, cardiovascular and metabolic disease, respiratory, renal and endocrine disorders, dermatology

International Economic Strategy Manager, Avastin (bevacizumab)
Roche Pharmaceuticals. Basel, Switzerland (www.roche.com): **since 09 / 2006**

- Implemented and designed key value messages as input of Global Value Dossiers for country affiliates
- Developed international strategic economic and pricing strategies under various assumptions
- Developed international reimbursement / payer strategies under various assumptions
- Delivered solid evidence based arguments for clinical and economic value stories
- Supported International Business and Lifecycle teams in strategic business decisions
- Supported International Business and Lifecycle teams in preparation of market launches in new therapeutic areas
- Management of outside vendors
- Leader of International Economic Strategy Team

EDUCATION

PhD – University of Zurich (Prof. Zweifel), Health Economics **04/2005-02/2007**
Thesis – 5 Essays in Health Economics

International PhD courses in Health Economics and Policy **2005-2006**
Network Health Economics (Greene, Zweifel, Manning, Fillippini, Jones; Holly, Johansson et al.)
Courses include Health Economics, Health Econometrics, Economic Evaluation, Politics

Master of Arts – Political Economy **1999-2004**
University of Potsdam, Germany
Eberhard-Karls University Tuebingen, Germany
Courses included Economic Theory, Financial Science, Economic Policy, Econometrics, Operations Research, Statistics

CERTIFICATIONS

Discrete Choice Analysis **2006**
Massachusetts Institute of Technology (USA), Swiss Institute of Technology (Switzerland), University of Laval (Canada), University of Boston (USA)

PhD course, Referee writing **2005**
University of Zurich (Switzerland)

Epidemiology Summer School **2005**
Harvard Medical School (USA), University of Muenster (Germany), University of Massachusetts (USA)

Markov Modeling Course **2004**
Harvard Medical School (USA)

Evidence Based Medicine **2004**
Cochrane Collaboration, University of Freiburg (Germany)

Health Technology Assessment **2004**
University of Bristol (UK)

SKILLS Software: Microsoft Office, SPSS, PrecisionTree, Sawtooth, STATA, Limdep, Biogeme; Languages: English, German fluent

Publications (December 2006):

Wardley AM, Cameron DA, Bell R, Erny S, Cohen C, Geary U, **Walzer S**, Gyldmark M. Cost-effectiveness analysis of adjuvant therapy with trastuzumab for early breast cancer. Lancet Oncology. Upcoming

Mueller E, **Walzer S**, Wiggenhauser A, Krone FA, Fassbinder W. Kosteneinsparungen in der Anämiebehandlung bei chronischen Nierenerkrankungen durch subkutane Applikation von Epoetin beta. [Cost savings in the treatment of anemia in chronic renal disease patients by subcutaneos application of Epoetin beta] Deutsches Ärzteblatt. Upcoming

Hitchcock W, Mellon M, Memran M, Morlotti L, Stern L, Parasuraman B, Ramachandran S, **Walzer S**. Caregiver preferences for delivery system in the treatment of pediatric asthma. Upcoming

Walzer S: Empirical comparison of utility derivation methods: Discrete-choice analysis and utility rating scores. Medical Decision Making;.submitted

Walzer S: Early retirement and the influence on health care budgets and insurance premiums in a diabetes population. Vascular Health and Risk Management; 2007; submitted

Walzer S: What do parents want from their child's asthma treatment?, Therapeutics and Clinical Risk Management; 2007; (in press)

Walzer S, Zweifel P: Willingness-to-pay for caregivers of children with asthma or wheezing conditions. Therapeutics and Clinical Risk Management; 2007 (in press)

Walzer S, Bergemann R: Cost-effectiveness: Biased results among current analyses?; Medical Decision Making; submitted

Walzer S, Mueller E, Casciano R, Freemantle N, Mathieu C, Bolinder B, Gerber R, Kvasz M, Bergemann R: External Validation of the Economic Assessment of Glycemic Control and Long-term Effects of Diabetes (EAGLE) Model; Diabetes Technology and Therapeutics. submitted

The Mt. Hood 4 modeling group: Computer modeling diabetes mellitus and its complications: A report on the fourth Mount Hood challenge meeting; Diabetes Care; accepted

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Casciano R, **Walzer S**, Mueller E: Krankheitsmodell am Beispiel Diabetes – das EAGLE Model [EAGLE – an example for a Diabetes Simulation Model]. Gesund ökon Qual manag Supplement 2; 2005: 10: S64 - S69

Walzer S: Der Zusammenhang von Geldpolitik und Aktienmärkten am Beispiel der USA, der EU und Japan. [The relationship between monetary policy and stock markets with examples from the United States, Europe and Japan] Diploma thesis, February 2004

Presentations (December 2006):

Hitchcock W, Mellon M, Memran M, Morlotti L, Stern L, Parasuraman B, Ramachandran S, **Walzer S**. Caregiver preferences for delivery system in the treatment of pediatric asthma. ACAAI congress, Philadelphia, USA, 2006

Walzer S: Applied Statistics – Disease modeling and Pharmacoeconomics. International Workshop on Statistical Methodology in Clinical R&D. Drug Information Association. Heidelberg 2006 (invited speaker)

Geary U, Lewis G, Erny S, Gyldmark G, Morlotti L, **Walzer S**. A sensitivity analysis of the cost per quality adjusted life year (QALY) of trastuzumab in the treatment of early breast cancer (EBC). ISPOR 9th European congress, Copenhagen, Denmark, 2006

Mueller E, **Walzer S**, Pieper L, Klotsche J, Stridde E. Comparing the development of a German diabetes population with respect to longterm outcomes using data from the DETECT study and the EAGLE diabetes simulation model. ISPOR 9th European congress, Copenhagen, Denmark, 2006

Walzer S, Mueller E, Janka HU, Huppertz E. Better HbA1c control with BOT versus CT avoids long-term micro-vascular complications in patients with type 2 diabetes: Model simulations with the DMM. ISPOR 9th European congress, Copenhagen, Denmark, 2006

Wardley AM, Cameron DA, Bell R, Erny S, Cohen C, Geary U, **Walzer S**, Gyldmark M. Cost-effectiveness analysis of adjuvant therapy with trastuzumab for early breast cancer. 31st ESMO congress, Istanbul, Turkey, 2006 (poster symposium)

Walzer S, Bergemann R, Freemantle N, Mathieu C, Kvasz M, Marchant N, Mueller E. External Validation of the Economic Assessment of Glycemic Control and Long-term Effects (EAGLE) Diabetes Model. European Association for the Study of Diabetes, Annual Meeting; Copenhagen, Denmark, 2006

Walzer S, Morlotti L, Mueller E. Comparison of two Budget Impact Modelling approaches: Impact of a new pharmaceutical product on annual health care expenditures and the impact on expenditures and insurance premiums. European Society for Medical Decision Making, Bi-Annual Meeting, Birmingham, United Kingdom, 2006

Mueller E., **Walzer S**, Rosery H, Bergemann R. Is the German Institute for Quality and Economics in the Health Care Setting (IQWIG) Prepared for Competitive Decision Making?. European Society for Medical Decision Making, Bi-Annual Meeting, Birmingham, United Kingdom, 2006

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Walzer S, Memran M, Morlotti L. Modeling and Estimating Preferences Over Treatments for Breast Cancer: Applied conjoint analysis with physicians in Europe and United States. ISPOR 11th Annual International Meeting; Philadelphia, USA, 2006

Walzer S: Applied Statistics – Disease modeling and Pharmacoeconomics. Basel Biometric Society. Winter talk, 2006

Walzer S, Maxion-Bergemann S, Bergemann R, Casciano R, Mueller E: Validation of the Economic Assessment of Glycemic Control and Long-term Effects (EAGLE) Diabetes Model, Society for Medical Decision Making, Annual Meeting, San Francisco, USA, 2005

Walzer S, Maxion-Bergemann S, Bergemann R, Casciano R, Mueller E: Validation of the Economic Assessment of Glycemic Control and Long-term Effects (EAGLE) Diabetes Model, ISPOR 8th European Congress, Florence, Italy, 2005

Mueller E, Maxion-Bergemann S, Gultyaev D, **Walzer S**, Bergemann R: EAGLE–Diabetes Model: Basic features and internal validation of simulating long-term diabetic outcomes and related costs; ISPOR 7th European Congress, Hamburg, 2004

Mueller E, **Walzer S**, Gultyaev D, Bergemann R, Casciano R: Mt Hood Diabetes Model Meeting IV, Presentation of EAGLE Version 1.2; Basel, CH, 2004

Mueller E, **Walzer S**, Maxion-Bergemann S, Gultyaev D, Bergemann R: EAGLE Model - Economic Assessment of Glycemic Control and Long-term Effects: A computer-simulation model for diabetes mellitus type 1 and type 2; Mt. Hood IV, Basel, CH, 2004